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January 8, 2018

VIA ECF

The Honorable Leda D. Wettre, U.S.M.J.
United States District Court for the District of New Jersey
Martin Luther King Jr. Federal Building & U.S. Courthouse
50 Walnut Street
Newark, New Jersey 07101

Re: *Celgene Corporation v. Zydus Pharmaceuticals (USA) Inc., et al.*,
Civil Action No. 17-2528 (SDW)(LDW)

Dear Judge Wettre:

This firm, together with Quinn Emanuel and Jones Day, represents Plaintiff Celgene Corporation ("Celgene") in the above-referenced matter. We write pursuant to Paragraphs 6, 8, and 14 of the Discovery Confidentiality Order ("DCO") (D.I. 64) to respectfully request that this Court preclude Dr. Brij Khera, Executive Vice President and Chief Legal Officer of Zydus Pharmaceuticals (USA) Inc., from receiving information designated Confidential or Highly Confidential under the DCO, or, in the alternative, compel Defendants to provide information concerning Dr. Khera's role and responsibilities, as well as other information relevant to the disclosure analysis.

I. Factual and Procedural Background

Under Paragraphs 6(a)(ii) and 6(b) of the DCO, each party may designate "two . . . in-house attorneys" to receive Confidential Information and Highly Confidential Information. D.I. 64 at 8-9, 11. On December 14, 2017, Zydus disclosed Dr. Khera as a potential recipient of Confidential Information and/or Highly Confidential Information (Confidential Information and Highly Confidential Information, together, "Protected Material") and included with its correspondence a signed Declaration of Compliance. (*See* Ex. A.) On December 22, 2017, Celgene timely objected to Zydus's request to show Dr. Khera Celgene's Protected Material based on its good-faith belief that Dr. Khera is involved in competitive decision making for Zydus and that he would be unable to comply with the DCO's explicit restriction on the use of Protected Material for anything other than this litigation, including for "any business, regulatory, commercial, or competitive purposes." D.I. 64 at 11. The parties subsequently met and

conferred, at which time Celgene asked Zydus to provide information concerning Dr. Khera's responsibilities as Executive Vice President and Chief Legal Officer so that Celgene could better assess the risk of inadvertent disclosure.[1] ***Zydus, however, refused to provide any details concerning Dr. Khera's roles and responsibilities, including details concerning whether Dr. Khera is a competitive decision maker***.[2] Instead, Zydus only provided an unsupported allegation that Dr. Khera is Zydus's only in-house lawyer. As described below, even if this were true, it does not control the inquiry. In view of Celgene's concerns regarding inadvertent use or disclosure of Celgene's competitively sensitive information, and Zydus's refusal to engage in a meaningful discourse, Celgene must submit this application to preserve its rights under the DCO and to avoid prejudicial disclosure of its Protected Material to a Zydus competitive decision maker.

II. Legal Standard

In determining whether in-house counsel should be permitted to have access to materials protected by a DCO, courts apply a two-step analysis.

First, courts determine "[w]hether an unacceptable opportunity for inadvertent disclosure exists." *U.S. Steel Corp. v. United States*, 730 F.2d 1465, 1468 (Fed. Cir. 1984). This requires consideration of facts on a counsel-by-counsel basis. *Id.* A key part of the inquiry looks to whether the in-house attorney is involved in competitive decision making. *See id*. at 1468 n.3. As the Federal Circuit has explained, competitive decision making is "shorthand for a counsel's activities, association, and relationship with a client that are such as to involve counsel's advice and participation in any or all of the client's decisions (pricing, product design, etc.) made in light of similar or corresponding information about a competitor." *Id*. Courts also consider a range of other factors, including, for example, whether the opposing parties are competitors, the size of the in-house attorney's company and its legal department, and safeguards in place to prevent inadvertent disclosure. *See, e.g.*, *PhishMe, Inc. v. Wombat Security Techs., Inc.*, C.A. No. 16-403, 2017 WL 4138961, at *4-8 (D. Del. Sept. 8, 2017) (discussing factors).

Second, courts "balance [the risk of disclosure] against the potential harm to the opposing party from restrictions imposed on that party's right to have the benefit of counsel of its choice." *In re Deutsche Bank Trust Co. Americas*, 605 F.3d 1373 (Fed. Cir. 2010). "In balancing these conflicting interests the district court has broad discretion to decide what degree of protection is required." *Id*.

III. Argument

This Court should not permit Dr. Khera, Executive Vice President and Chief Legal Office of Zydus Pharmaceuticals (USA) Inc., to have access to Celgene's Protected Material, especially

[1] Paragraph 8 of the DCO expressly prohibits the use of Protected Material "for any business, regulatory, commercial, or competitive purposes." D.I. 64 at 11-12.

[2] Zydus also dismissed Celgene's good-faith requests for additional information by repeatedly stating that Celgene bears the burden of proof on this issue under the DCO. This Court should not permit Zydus to simultaneously block access to relevant facts where Celgene has a colorable concern and also bears the burden of proof.

given Zydus's refusal to provide a single detail regarding Dr. Khera's roles and responsibilities, including details concerning whether he is involved in competitive decision making.

A. Dr. Khera Should Not Have Access to Celgene's Protected Material

Celgene focuses on and invests heavily in the discovery and development of products for the treatment of severe and life-threatening conditions. Celgene seeks to protect its confidential, competitively-sensitive information from Zydus's competitive use. Providing Dr. Khera with access to Celgene's Protected Material would create an unacceptable risk of inadvertent use or disclosure. The balance of harms weighs in favor of precluding Dr. Khera from accessing such material.

i. Providing Dr. Khera With Access to Celgene's Protected Material Would Create an Unacceptable Risk of Inadvertent Use or Disclosure

The risk of inadvertent use or disclosure of Celgene's Protected Material is unacceptable. Celgene maintains that Dr. Khera, in his role as Executive Vice President and Chief Legal Officer of Zydus Pharmaceutical (USA) Inc., will be unable to comply with Paragraph 8 of the DCO.[3] Notably, Zydus has refused to provide ***any*** details concerning Dr. Khera's responsibilities and has refused to state its position as to whether Dr. Khera is a competitive decision maker.

Based on that information, it is likely that Dr. Khera is involved in competitive decision making. *First*, Dr. Khera's title of Executive Vice President and Chief Legal Officer raises concern. Courts have determined that individuals with such titles, in view of their responsibilities, present a risk of inadvertent disclosure. *See, e.g.*, *Federal Trade Commission v. Sysco Corp.*, 83 F. Supp. 3d 1, 3-4 (D.D.C. 2015) (precluding Chief Legal Officer and Executive Vice President of Corporate Affairs' access to confidential information, noting "close proximity to [defendant's] competitive decision-making" and counsel's "business development responsibilities"). *Second*, searches of publicly available information show that Dr. Khera signs licensing and other business agreements, which supports the likelihood that Dr. Khera directs strategic decisions regarding intellectual property and project selection. (*See* Exs. B, C.) *Third*, he is listed as a named inventor and prosecuting attorney on patents that appear to relate to Zydus ANDA products that have been the subject of patent litigation. (*See* Ex. D (patent entitled, "Method for preparation of pitavastatin and pharmaceutical acceptable salts thereof"); Ex. E (patent entitled, "Pitavastatin calcium and process for its preparation"); Ex. F (patent entitled, "Method of preparation of pitavastatin and pharmaceutical acceptable salts thereof"); Ex. G (complaint concerning Zydus's proposed pitavastatin drug product).) Notably, a "Brij Khera" is also a named inventor on a patent belonging to Cadila Healthcare Limited—the other Defendant in this case and Zydus's corporate parent—which is purportedly directed to an "amorphous form

[3] Celgene in no way presumes or suggests that Dr. Khera would intentionally disclose or misuse Celgene's Protected Material. Rather, the primary concern, as courts have recognized, is ***inadvertent*** disclosure, such that once one learns of a competitor's confidential information, "it becomes very difficult . . . to completely insulate that information from the thought process involved in providing one's client advice on competition-related issues." *PhishMe*, 2017 WL 4138961, at *2 n.6.

of apremilast." (*See* Ex. H (U.S. Patent No. 9,351,957).) Apremilast is the active pharmaceutical ingredient in Otezla®, another of Celgene's drug products that is not at issue in this litigation, but that may be the subject of a future Zydus ANDA. Based on these publicly available facts, Dr. Khera's responsibilities at Zydus appear to be broad and substantial. Accordingly, it is likely that Dr. Khera is involved in strategic and competitive decision making. ***Zydus has refused to provide any information regarding Dr. Khera's roles and responsibilities.***

The risk of inadvertent disclosure is exacerbated by the fact that Celgene and Zydus are direct competitors. *See DSM Desotech, Inc. v. Momentive Specialty Chemicals, Inc.*, 15-70, 2016 WL 8193590, at *8 (S.D. Ohio May 31, 2016). Here, Zydus seeks to make a generic version of Celgene's Revlimid® drug product that, if approved, will directly compete with Revlimid®. Zydus's business also focuses on developing and marketing generic drug products,[4] and Zydus may therefore submit ANDAs concerning other Celgene products in the future. This includes Otezla®, a product that Defendants are clearly working on, as demonstrated by the Cadila patent focusing on the active ingredient in that product, and which patent lists "Brij Khera" as an inventor. In short, if Celgene produced sensitive financial or research-and-development documents containing Celgene's Protected Material, the inadvertent use of such information could impact Zydus's financial or product-design strategy for the generic product at issue in this case, as well as for other potential generic products. Such inadvertent use would significantly prejudice Celgene and would defeat the purpose of the DCO in this case. *See also U.S. Steel*, 730 F.2d at 1468 ("Inadvertence, like the thief-in-the-night, is no respecter of its victims.").

Zydus refused to discuss Dr. Khera's job responsibilities during the parties' meet and confer, and would not confirm or deny whether Dr. Khera is a competitive decision maker. Instead, Zydus represented only that Dr. Khera is purportedly the sole in-house lawyer at Zydus. As an initial matter, it is unclear whether this is accurate. According to LinkedIn, Zydus appears to employ at least one other attorney, whose title is "General Counsel and Chief Compliance Officer." (*See* Ex. I.) And counsel has not made any representations regarding the legal department of Cadila, the other Defendant in this case, which is Zydus's corporate parent. But even assuming that counsel's representation regarding Dr. Khera is accurate, as the only in-house attorney, Dr. Khera likely takes on a range of matters aside from managing litigation, all of which could lead to inadvertent disclosure. For example, if, in addition to his role in overseeing litigation, Dr. Khera is responsible for negotiating supply or pricing contracts, then there exists a significant risk that Celgene's Protected Material will inform the parameters of those contracts, potentially to Celgene's detriment. Also, providing Dr. Khera with Celgene's Protected Material could place him in the untenable position of having to refuse to advise Zydus or risk disclosing Celgene's Protected Material.

Based on the foregoing, there exists an unacceptable risk of inadvertent disclosure and the risk of harm to Celgene resulting from such disclosure is both real and significant.

[4] *See* http://www.zydususa.com (stating that Zydus is "focusing on providing our customers outstanding service and high-quality, affordable generics.")

ii. Balancing the Unacceptable Risk of Disclosure Against Any Harm to Zydus Militates Against Providing Dr. Khera With Access to Celgene's Protected Material

The unacceptable risk of inadvertent disclosure of Celgene's highly sensitive Protected Material outweighs any nominal harm that Zydus might experience. Even assuming that Dr. Khera is Zydus's only in-house attorney, Zydus has not offered any information to suggest that Dr. Khera's lack of access to Celgene's Protected Material will impede Zydus's ability to litigate through its competent outside counsel. Should Zydus offer any such arguments, Celgene requests the opportunity to respond.

In light of the unacceptable risk of disclosure as balanced against the absence of prejudice to Zydus if Dr. Khera cannot access Celgene's Protected Material, Dr. Khera should be precluded from accessing Celgene's sensitive and confidential information.

B. In the Alternative, This Court Should Sustain Celgene's Objection and Order Defendants to Provide Relevant Information

If Your Honor is not inclined to grant Celgene's request outright, then Celgene respectfully requests that the Court order Defendants to provide additional information (including an affidavit from Dr. Khera) relevant to the disclosure analysis and, in the meantime, preclude Dr. Khera from having access to Protected Material. As mentioned above, Zydus has refused to provide Celgene with ***any*** information concerning Dr. Khera's responsibilities.

IV. Conclusion

For the foregoing reasons, Celgene respectfully requests that the Court preclude Dr. Khera from accessing Celgene's Protected Material or, in the alternative, order Defendants to provide additional information and, in the meantime, preclude Dr. Khera from having access to Protected Material.

Thank you for Your Honor's kind attention to this matter.

Respectfully yours,

William C. Baton

William C. Baton

Exhibits

cc: All Counsel (via e-mail)

EXHIBIT A

EXHIBIT A

CELGENE CORPORATION, **Plaintiff,** **v.** **ZYDUS PHARMACEUTICALS (USA) INC. and CADILA HEALTHCARE LIMITED,** **Defendants.**	**Civil Action No. 17-2528 (SDW)(LDW)**

DECLARATION OF COMPLIANCE

I, BRIJ KHERA do declare and state as follows:

1. I live at PLAINSBORO, NEW JERSEY. I am employed as (state position) EVP & Chief Legal Officer by (state name and address of employer) Zydus Pharmaceuticals (USA) Inc., 73 Route 31N, Pennington, NJ 08534

2. I have read the Discovery Confidentiality Order entered in this case, a copy of which has been given to me.

3. I understand and agree to comply with and be bound by the provisions of the Discovery Confidentiality Order, including that upon receipt of any Confidential Information or Highly Confidential Information, I will be personally subject to it, and to all of its requirements and procedures.

4. I agree that I will be subject to the jurisdiction of the United States District Court for the District of New Jersey for purposes of enforcement of the Discovery Confidentiality Order.

5. I understand that unauthorized disclosure of any designated Confidential Information or Highly Confidential Information, or its use for any purpose other than this

litigation, may constitute contempt of this Court and may subject me to sanctions or other remedies that may be imposed by the Court and or potential liability in a civil action for damages by the producing party.

6. At the final termination of this litigation, I will return to counsel or destroy all documents or things consisting of or containing Confidential Information or Highly Confidential Information.

7. I declare, as provided by 28 U.S.C. Section 1746, under penalty of perjury, under the laws of the United States of America, that the foregoing is true and correct.

Executed this 12th day of December, 2017.

Brij Khera

EXHIBIT B

EX-10.4 5 d384792dex104.htm SETTLEMENT AND LICENSE AGREEMENT BY AND AMONG SOMAXON PHARMACEUTICALS

Exhibit 10.4

CERTAIN CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT (INDICATED BY ASTERISKS) HAS BEEN OMITTED AND FILED SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO A REQUEST FOR CONFIDENTIAL TREATMENT.

SETTLEMENT AND LICENSE AGREEMENT

This SETTLEMENT AND LICENSE AGREEMENT (this "Agreement") is hereby entered into on July 18, 2012 (the "Execution Date") by and among Somaxon Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware ("Somaxon"), ProCom One, Inc., a corporation organized under the laws of the State of Texas ("ProCom"), (Somaxon and ProCom are collectively "Plaintiffs"), Zydus Pharmaceuticals (USA), Inc., a corporation organized and existing under the laws of the State of New Jersey ("Zydus"), and Cadila Healthcare Limited, a company organized and existing under the laws of India ("Cadila") (Zydus and Cadila are collectively "Defendants"; each Plaintiff and each Defendant is a "Party").

RECITALS

WHEREAS, Somaxon is the holder of New Drug Application ("NDA") No. 22-036 (the "Somaxon NDA"), which was approved by the United States Food and Drug Administration ("FDA") for the manufacture and sale of (a) an oral tablet containing as its sole active ingredient 3 mg doxepin hydrochloride, and (b) an oral tablet containing as its sole active ingredient 6 mg doxepin hydrochloride, in each of cases (a)-(b), that is marketed and sold by Somaxon in the Licensed Territory (as defined below), under the trade name SILENOR® (the "Silenor Products");

WHEREAS, the formulation and dosing of the Silenor Products are covered by certain claims of the Licensed Patents (as defined below);

WHEREAS, ProCom owns one of the Licensed Patents and Somaxon is the exclusive licensee of such Licensed Patent in the Licensed Territory, and Somaxon owns the other Licensed Patent;

WHEREAS, the Licensed Patents are listed in the Orange Book (as defined below) for each of the strengths of the Silenor Products approved by the FDA under the Somaxon NDA;

WHEREAS, pursuant to 21 USC § 355(j) Zydus filed Abbreviated New Drug Application ("ANDA") No. 202761 (the "Zydus ANDA") with respect to a 3 mg doxepin hydrochloride product and a 6 mg doxepin hydrochloride product, and such ANDA is currently pending before FDA;

WHEREAS, Plaintiffs initiated an action against Defendants in the United States District Court for the District of Delaware (the "District Court") under 35 USC § 271(e) alleging infringement of the Licensed Patents, in a case captioned *Somaxon Pharmaceuticals, Inc. and ProCom One, Inc. v. Zydus Pharmaceuticals USA, Inc. and Cadila Healthcare Limited (d/b/a Zydus Cadila)*, Civil Action No. 1:11-cv-00537-RGA (D. Del.) (the "Litigation");

WHEREAS, Defendants have asserted certain affirmative defenses and counterclaims in the Litigation;

WHEREAS, the Parties have agreed to resolve their disputes relating to the Litigation through this Agreement, in order to avoid further litigation and the attendant risk, associated fees, costs and expenses thereof;

WHEREAS, this Agreement is the only agreement between the Parties related to the settlement of the Litigation, and no Party has received any consideration from any other Party for its entry into this Agreement other than that which is described in this Agreement; and

WHEREAS, as a result of this Agreement there will be an opportunity for pro-competitive generic competition for doxepin hydrochloride products for human use, which competition otherwise may not have existed until the expiration of the Licensed Patents and any applicable period of exclusivity.

NOW, THEREFORE, in consideration of the mutual agreements herein contained, the sufficiency and receipt of which are hereby acknowledged, the Parties hereto, intending to be legally bound hereby, agree as follows:

1. DEFINITIONS

1.1 "Affiliate" means, with respect to an entity, any other entity that controls, is controlled by, or is under common control with such first entity, where "control" means (a) in the case of corporate entities, direct or indirect ownership of at least fifty percent (50%) of the stock or shares having the right to vote for the election of directors, and (b) in the case of non-corporate entities, direct or indirect ownership of at least fifty percent (50%) of the equity interest with the power to direct the management and policies of such non-corporate entities.

1.2 "Asserted Claims" means (i) with respect to an oral tablet containing 3 mg doxepin hydrochloride, claims nos. 1, 2, 3, 5, 6, 24, 25, 27, and 28 of the '229 patent and claims nos. 1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 20, 21, 22, 23 and 24 of the '307 patent, and (ii) with respect to an oral tablet containing 6 mg doxepin hydrochloride, claims nos. 1, 2, 3, 5, 6, 24, 25, 27, and 28 of the '229 patent and claims nos. 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 18, 19, 21, 22, 23 and 24 of the '307 patent.

1.3 "Business Day" means a day on which the banks in the State of Delaware are permitted to be open.

1.4 "Commercial Sale Date" means, on a dosage strength-by-dosage strength basis, the date on which a doxepin hydrochloride tablet product containing as its sole active ingredient either 3 mg or 6 mg doxepin hydrochloride is first commercially sold in the Licensed Territory by a Third Party (excluding (i) any Person acting in concert with or under license from Zydus or its Affiliates or (ii) any Person purchasing the Zydus ANDA) pursuant to an ANDA referencing the Somaxon NDA under a license or covenant not to sue granted to such Third Party by Plaintiffs.

1.5 "Final Decision Date" means, on a dosage strength-by-dosage strength basis, the date of a final decision of a federal court from which no appeal has been or can be taken, excluding any petition for a writ of certiorari or other proceedings before the United States Supreme Court, holding each of the relevant Asserted Claims unenforceable or invalid.

1.6 "Generic Equivalent" means, on a dosage strength-by-dosage strength basis, a pharmaceutical product containing doxepin hydrochoride as its sole active ingredient that is AB-rated to the equivalent dosage strength Silenor Product and has received FDA approval for marketing in the Licensed Territory pursuant to an ANDA referencing Somaxon's NDA No. 22-036.

1.7 "Generic Product" means each of the following: (a) a product containing as its sole active ingredient 3 mg doxepin hydrochloride, and (b) a product containing as its sole active ingredient 6 mg doxepin hydrochloride, in each of cases (a)-(b), that is a generic version of the corresponding Silenor Product.

1.8 "License Date" means, on a dosage strength-by-dosage strength basis, the earlier of:

(a) 180 days after the Commercial Sale Date;

(b) 180 days after the Final Decision Date; or

(c) immediately upon the Commercial Sale Date or Final Decision Date, provided that (i) under 21 U.S.C. § 355 (j)(5)(D)(ii), all first applicants who have filed ANDAs referencing Somaxon's NDA No. 22-036 forfeit the 180-day exclusivity periods and (ii) Plaintiffs have not entered into an exclusive or semi-exclusive license with any first applicant that would contractually preclude Defendants' manufacturing, having manufactured, offering for sale, importing, marketing or selling the relevant dosage strength of the Zydus Generic Product upon the Commercial Sale Date or Final Decision Date. This clause (c) shall not apply in the event of an occurrence under 21 U.S.C. § 355 (j)(5)(D)(i)(III);

provided that the License Date shall be subject to modification pursuant to Section 9.1.

1.9 "Licensed Patents" means:

(a) U.S. Patent No. 6,211,229 (together with all reissues, reexaminations and patent and regulatory extensions thereof, "the '229 patent"), and

(b) U.S. Patent No. 7,915,307 (together with all reissues, reexaminations and patent and regulatory extensions thereof, "the '307 patent");

together with all continuations, continuations-in-part or divisionals of any of the aforementioned patents.

1.10 "Licensed Territory" means the United States of America, and its territories, districts and possessions, including the Commonwealth of Puerto Rico.

1.11 "Marketing Partner" means (a) a sublicensee (if permitted by Plaintiffs) or (b) a Person from whom a Defendant or its Affiliate gets a payment based on sales or other dispositions of a Zydus Generic Product by such Person.

1.12 "Net Revenues" means, on a dosage strength-by-dosage strength basis, the sum of the gross amount invoiced for the sale or other disposition of the relevant Zydus Generic Product by Defendants or any of their Affiliates or Marketing Partners in the Licensed Territory, less the following items to the extent applicable to such Zydus Generic Product: (a) one-time per customer stocking allowances, any and all slotting allowances, inventory price adjustments or Medicaid discounts and any and all rebates, charge-backs, quantity and cash discounts, and other usual and customary rebates or discounts, in each case actually granted to customers or governmental or regulatory authorities; (b) amounts refunded, repaid or credited by reason of rejections or returns of goods, (c) any sales, excise, turnover, inventory, value-added, and similar taxes and duties assessed on applicable sales to the extent they are recorded in gross amount invoiced, and (d) transportation charges (including insurance costs) and handling charges to the extent they are invoiced and included in gross sales. Net Revenues will be determined in accordance with U.S. Generally Accepted Accounting Principles applied in a manner consistent with Defendants' or their relevant Affiliates' or Marketing Partners' customary practices. For the avoidance of doubt, sales of Zydus Generic Products between or among Defendants and their Affiliates and Marketing Partners for resale shall not be included within Net Revenues; provided, however, that any subsequent sale of such Zydus Generic Products by Defendants or such Affiliates or Marketing Partners to a Third Party in the Licensed Territory, or any other payment received by Defendants or its Affiliates or Marketing Partners from such Third Parties relating to the sale of Zydus Generic Products in the Licensed Territory, shall be included within Net Revenues.

1.13 "Orange Book" means the publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations," in electronic or hard copy form, maintained by the FDA, including all supplements thereto.

1.14 "Paragraph IV Notice Letter" means a written notice including any "patent certification" filed in the United States under 21 U.S.C. §355(j)(2)(A)(vi)(IV).

1.15 "Person" means any individual, partnership, association, corporation, limited liability company, trust, governmental authority or other legal person or entity.

1.16 "Pre-Marketing" means engaging in outreach to potential purchasers to inform them that Defendants will be offering to sell and selling the Zydus Generic Product for distribution in the Licensed Territory on or after the License Date (including, for example, notification to customers regarding the Zydus Generic Product and engaging customers in non-binding pricing or contracting activities).

1.17 "Royalty Period" means, on a dosage strength-by-dosage strength basis, the period beginning on the applicable License Date and ending when every Asserted Claim which covers such dosage strength of the Zydus Generic Product has expired or been held unenforceable or invalid pursuant to a Final Decision.

1.18 "Third Party" means a Person other than the Parties or any of their Affiliates.

1.19 "Total Doxepin Sales" means, on a dosage strength-by-dosage strength basis, the total gross dollar sales of doxepin hydrochloride tablets containing 3 mg or 6 mg (as applicable) doxepin hydrochloride active ingredient sold pursuant to an NDA or ANDA *** in or for the Licensed Territory, with the total gross dollar sales data determined from publicly available information (such as data provided by IMS Health Incorporated, Fairfield, Connecticut (together with its Affiliates, "IMS") or, if not so publicly available, then as reasonably determined by Plaintiffs).

1.20 "Trademark" means the trademark SILENOR®.

1.21 ***.

1.22 "Zydus Generic Product" means a Generic Product that is manufactured or marketed under the Zydus ANDA.

1.23 ***.

2. DISMISSAL AND RELATED FILINGS

2.1 Termination of Litigation.

(a) On or before the third (3rd) Business Day after the Execution Date, Plaintiffs and Defendants shall file with the District Court a stipulated consent judgment and joint motion to dismiss the Litigation, substantially in the form attached as Exhibit A (the "Judgment and Dismissal"), with each Party to bear its own fees and costs.

(b) The date on which the Judgment and Dismissal is entered by the District Court shall be the "Effective Date". The provisions of Sections 1 (to the extent necessary to interpret the other sections listed in this Section 2.1(b)), 2, 10, 11 and 14 of this Agreement shall become effective upon the Execution Date, while the remaining provisions of this Agreement shall become effective upon the Effective Date.

2.2 FTC/DOJ Filings.

(a) Within ten (10) days following the Execution Date, the Parties shall file with the U.S. Federal Trade Commission, Bureau of Competition ("FTC") and the Antitrust Division of the U.S. Department of Justice ("DOJ") this Agreement and any notifications to be filed pursuant to Title XI of the Medicare Prescription Drug Improvement and Modernization Act (Subtitle B — Federal Trade Commission Review) and any other applicable law. The Parties shall make additional timely filings as required by law.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

(b) The Parties shall use all commercially reasonable efforts to coordinate the foregoing filings and any responses thereto, to make such filings promptly and in good faith and to respond promptly and in good faith to any requests for additional information made by either of such agencies, and to coordinate any necessary or desirable joint presentations. Each Party reserves the right to communicate with the FTC or DOJ regarding such filings as it believes appropriate. Each Party shall keep the other Party reasonably informed of such communications and shall not disclose any confidential information of the other Party without such other Party's consent, which will not be unreasonably withheld or delayed.

3. RELEASE OF CLAIMS

3.1 In settlement of the Litigation, and in consideration of the releases, representations, warranties and covenants contained in this Agreement, as of the Effective Date, each Party and its respective parents, subsidiaries and Affiliates, on behalf of themselves and their respective predecessors, successors, administrators, attorneys, assigns, agents, officers, employees, shareholders, directors, representatives and all other Persons claiming by, through and under them, do fully, finally and forever release, relinquish, acquit and discharge each other Party and each of its respective parents, subsidiaries and Affiliates, on behalf of themselves and their respective predecessors, successors, administrators, attorneys, assigns, agents, officers, employees, shareholders, directors and representatives (collectively, the "Releasees"), from any and all claims, demands, damages, liabilities, obligations, and causes of action accruing prior to the Effective Date (including costs, expenses and attorneys' fees), that were or could have been filed in the Litigation, whether known or unknown, to the extent arising out of, related to, or in connection with: (a) the Litigation, (b) the Zydus ANDA or its filing, or (c) the Zydus Generic Products.

3.2 Each Party hereby expressly waives any and all provisions, rights and benefits conferred by §1542 of the California Civil Code, or by any law of the United States or principle of common law that is similar, comparable or equivalent to §1542 of the California Civil Code, with respect to the matters released in this Section 3. §1542 of the California Civil Code provides as follows:

> A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS WHICH THE CREDITOR DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE, WHICH IF KNOWN TO HIM OR HER MUST HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR.

3.3 Each Party represents, warrants and covenants that it had not, prior to the Effective Date, assigned or transferred, and will not assign or otherwise transfer, to any Person any matters released by such Party as set forth in this Section 3 (except that the foregoing shall not prohibit an assignment of this Agreement pursuant to Section 14.3), and such Party agrees to indemnify and hold harmless the other Party and its Releasees from and against all such released matters arising from any such alleged or actual assignment or transfer.

3.4 For the sake of clarity, this Section 3 shall not prevent or impair the right of a Party to bring a proceeding in court or any other forum for a breach of this Agreement or any representation, warranty or covenant herein.

4. ADMISSIONS AND COVENANTS

4.1 Defendants, on behalf of themselves and their Affiliates, acknowledge and agree that the Asserted Claims relevant to each Zydus Generic Product: (a) would be infringed by the making, having made, importation, use, offer for sale or sale in, or importation into, the Licensed Territory of such Zydus Generic Product other than as permitted by this Agreement; and (b) are valid and enforceable solely as to such Zydus Generic Product.

4.2 Defendants, on behalf of themselves and their Affiliates, agree not to challenge the validity, enforceability or patentability of any of the Licensed Patents or to seek reexamination of those patents in any court or administrative agency (including the United States Patent and Trademark Office) having jurisdiction to consider the issue. Defendants also agree, on behalf of themselves and their Affiliates, not to intentionally assist others, whether directly or indirectly, in challenging the validity, enforceability or patentability of any of the Licensed Patents, or in seeking reexamination of such patents, in any court or administrative agency having jurisdiction to consider the issue. Nothing herein will prevent Defendants and their Affiliates from responding to subpoenas from courts or administrative agencies or filing a "paragraph IV" certification against the Licensed Patents to the extent they are listed in the Orange Book for a product other than the Silenor Products.

5. LICENSE AND RELATED RIGHTS

5.1 License. Plaintiffs hereby grant to Defendants, effective on and from the applicable License Date, a non-exclusive, non-transferable (except in connection with an assignment of this Agreement pursuant to Section 14.3), royalty-bearing and non-sublicenseable license under the Licensed Patents, to make, have made, import, offer for sale, market and sell the relevant Zydus Generic Product in the Licensed Territory to Defendants' and their Affiliates' distributors, wholesalers, pharmacies and other customers in the Licensed Territory for ultimate resale (whether directly or indirectly through multiple levels of distribution) to consumers in the Licensed Territory.

5.2 Preparatory License. In addition, Plaintiffs hereby grant to Defendants, (a) effective on and from the date *** days prior to the applicable License Date (the "Manufacturing Date"), a non-exclusive, non-transferable (except in connection with an assignment of this Agreement pursuant to Section 14.3), and non-sublicenseable license under the Licensed Patents, to make, have made and import the relevant Zydus Generic Product in the Licensed Territory in preparation for sales on and after the License Date pursuant to Section 5.1, and (b) effective on and from the date *** days prior to the applicable License Date (the "Pre-Marketing Date"), a non-exclusive, non-transferable (except in connection with an assignment of this Agreement pursuant to Section 14.3), and non-sublicenseable license under the Licensed Patents, to conduct Pre-Marketing in the Licensed Territory in preparation for offers for sale and sales on and after the License Date pursuant to Section 5.1.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

5.3 Covenant to Plaintiffs. In return for Plaintiffs' grant of the license and other rights in Sections 5.1 and 5.2, Defendants, on behalf of themselves and their Affiliates, agree not to (i) make or have made a Generic Product in the Licensed Territory prior to the applicable Manufacturing Date, (ii) import a Generic Product into the Licensed Territory prior to the applicable Manufacturing Date, (iii) conduct Pre-Marketing (for such purpose, replacing Generic Product for Zydus Generic Product in the definition of "Pre-Marketing") for a Generic Product in the Licensed Territory prior to the applicable Pre-Marketing Date or (iv) market (other than as permitted in Section 5.2(b)), offer for sale or sell a Generic Product in the Licensed Territory prior to the applicable License Date.

5.4 Acknowledgement. Defendants acknowledge that, notwithstanding the definition of the License Date, Manufacturing Date and Pre-Marketing Date, Defendants may not be able to legally exploit the license and other rights granted pursuant to Sections 5.1 and 5.2 with respect to the Zydus Generic Products for various reasons, including exclusivity granted by the FDA to Third Parties or lack of regulatory approval for the Zydus ANDA by the FDA.

5.5 No Restriction on Right to Grant ***: Defendants acknowledge and agree that nothing herein shall restrict the ability of Plaintiffs to grant to a Third Party who has *** for a period of 180 days after first commercial sale ***. Plaintiffs shall inform Defendants of the date *** in writing within thirty (30) days after entering into such license.

5.6 Retained Rights. Except for the license and other rights granted pursuant to this Agreement, all other rights to any intellectual property or regulatory exclusivities or approvals held by Plaintiffs or any of their Affiliates are hereby retained by Plaintiff and their Affiliates. For the sake of clarity, this Agreement does not grant to Defendants or their Affiliates any right to use any corporate names, logos or trademarks (including the Trademark) of any Plaintiff or any of their Affiliates inside or outside the Licensed Territory.

6. ***

6.1 On a dosage strength-by-dosage strength basis, in the event that one or more Third Party(ies) *** and if Defendants ***, and if Plaintiffs ***, then:

(a) Defendants shall, immediately upon *** until the applicable date specified in Section 5.1 or 5.2, and shall ***; and

(b) Defendants shall pay to Somaxon as liquidated damages, and not as a penalty, for Net Revenues of the Zydus Generic Products (on a dosage strength-by-dosage strength basis) in or for the Licensed Territory ***:

(i) If the *** is *** or more for such ***, Defendants shall pay to Somaxon *** of Net Revenues of the relevant Zydus Generic Products in or for the Licensed Territory ***;

(ii) If the *** is *** or more but less than *** for such ***, Defendants shall pay to Somaxon *** of Net Revenues of the relevant Zydus Generic Products in or for the Licensed Territory ***;

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

(iii) If the *** is *** or more but less than *** for such ***, Defendants shall pay to Somaxon *** of Net Revenues of the relevant Zydus Generic Products in or for the Licensed Territory ***; and

(iv) If the *** is less than *** for such ***, Defendants shall pay to Somaxon *** of Net Revenues of the relevant Zydus Generic Products in or for the Licensed Territory ***.

6.2 Defendants shall pay the amounts set forth in Section 6.1(b) within thirty (30) days after the end of the applicable ***, and such payment (the "Liquidated Damages Payment") shall be accompanied by a report providing in reasonable detail an accounting of all Net Revenues of the relevant Zydus Generic Products, a calculation of the deductions from gross invoice price to such Net Revenues and the calculation of the applicable royalties under Section 6.1(b). Notwithstanding the foregoing, in the event that a *** then (i) the ***, and (ii) Somaxon shall promptly ***.

6.3 The Parties understand and agree that the damages to Plaintiffs of a *** subsequent sales is uncertain and that the amounts set forth in Section 6.1(b) are a genuine estimate of the loss the Parties believe would be suffered by Plaintiffs as a result of ***.

6.4 The foregoing is not a limitation of Plaintiffs' right to obtain damages or any other remedy with respect to *** prior to the License Date under any circumstances other than a *** and/or ***. However, the remedies set forth in this Section 6 shall be the exclusive remedies of the Plaintiffs with respect to any ***. Notwithstanding anything herein to the contrary, the Plaintiffs acknowledge and agree that any *** is not a violation of the Judgment and Dismissal and the Plaintiffs shall not bring any claim asserting a violation of the Judgment and Dismissal (including, by way of example and not limitation, any claim for contempt with respect to the Judgment and Dismissal) based thereupon.

7. ROYALTY PAYMENTS

7.1 With respect to each calendar quarter (or part thereof) during the Royalty Period, on a dosage strength-by-dosage strength basis, Zydus shall pay Somaxon a royalty of *** of Net Revenues of Zydus Generic Products made during such calendar quarter (or, if applicable, the portion thereof that falls within the Royalty Period).

7.2 Within thirty (30) days after the end of each calendar quarter for which royalties are payable by Zydus under Section 7.1, Zydus shall submit to Somaxon a report (the "Quarterly Report"), providing in reasonable detail an accounting of all Net Revenues by Zydus and its Affiliates, including in each case, an accounting of all unit sales of the Zydus Generic Products, a calculation of the deductions from gross invoice price to Net Revenues made during such calendar quarter and the calculation of the applicable royalties under Section 7.1. Zydus shall, at the time it submits the Quarterly Report, pay to Somaxon all amounts due under Section 7.1, as indicated in the applicable report.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

8. PAYMENT TERMS

8.1 Any payments due pursuant to Sections 6 or 7 shall be made by wire transfer to an account specified by Plaintiffs in writing.

8.2 Defendants shall maintain its books and records with respect to Net Revenues, and will cause its Affiliates and Marketing Partners to maintain their books and records with respect to Net Revenues, for a period of three (3) calendar years after the calendar year to which they relate. Plaintiffs, through a nationally-recognized firm of independent certified public accountants mutually and reasonably acceptable to the Parties, shall have the right to audit such books and records on reasonable advance notice to Defendants, no more than once per calendar year. If Zydus has overpaid any amounts hereunder, the overpayment shall be credited against amount due hereunder. If Zydus has underpaid any amounts hereunder, Zydus shall pay the relevant amount (net of any credits for overpayment) within thirty (30) days after receipt of the auditor's report. The audit shall be at Plaintiffs' cost and expense unless the underpayment exceeds five percent (5%) of the amount owed with respect to any calendar year, in which case Zydus shall promptly reimburse such costs and expenses.

9. MOST FAVORED NATION

9.1 On a dosage strength-by-dosage strength basis, in the event a Plaintiff or any of its Affiliates ***, then this Agreement shall be automatically amended to ***, and Plaintiffs shall inform Defendants of such *** in writing within thirty (30) days after ***. Defendants acknowledge, for purposes of this Section 9.1, the provisions of Section 5.5.

9.2 On a dosage strength-by-dosage strength basis, in the event a Plaintiff or any of its Affiliates ***, then Plaintiffs shall inform Defendants in writing of such *** within thirty (30) days after ***, and this Agreement shall be automatically amended to ***.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

10. CONFIDENTIALITY

10.1 Each of the Parties shall keep the terms of the Agreement and the underlying settlement confidential, using at least the level of care it uses for its own proprietary information (but no less than reasonable care), and shall not disclose to any Third Party (other than (a) such Party's financial advisors, legal advisors, and insurers, and (b) parties and their counsel in litigation or anticipated litigation with Plaintiffs over any of the Licensed Patents solely for purposes of disclosing, in connection with settlement negotiations, those provisions herein addressing the relevant License Date, royalty rates and liquidated damages provisions, in each such case subject to appropriate confidentiality protections), except as provided below or as required by law (including disclosures required by the FTC and/or the DOJ).

10.2 No Party shall issue or make any public announcement, press release, or other public disclosure regarding this Agreement or the subject matter or terms of the settlement, except as required by law or the rules of a stock exchange on which the securities of the disclosing Party are listed. In the event a Party is, in the opinion of its counsel, required to make a public disclosure by law or the rules of a stock exchange on which its securities are listed, such Party shall, if permitted by law, submit the proposed disclosure in writing to the other Party a reasonable period prior to disclosure, and such Party shall provide any such comments promptly, but in any case within two (2) Business Days of its receipt of such disclosure.

10.3 Notwithstanding Sections 10.1 and 10.2, Defendants may communicate with (a) the FDA on a confidential basis prior to the applicable License Date concerning the approval of the Zydus ANDA, and the licenses and waivers provided for herein, and (b) its manufacturers on a confidential basis (using at least the level of care it uses for its own proprietary information, but not less than reasonable care), prior to the applicable License Date to the extent necessary to enable such manufacturers to manufacture Zydus Generic Products in accordance with the terms and conditions set forth in this Agreement.

10.4 Defendants acknowledge that (a) Plaintiffs are currently engaged in ANDA-related patent litigations with various Third Parties concerning the Licensed Patents and may become engaged in future patent litigation concerning infringement of the Licensed Patents and (b) such parties may request a copy of this Agreement in connection with discovery. Notwithstanding Sections 10.1 and 10.2, Defendants agree to Plaintiff's production of this Agreement under the highest level of confidentiality and protection offered in the applicable protective order; provided, that Plaintiffs give Defendants notice of any such discovery request no less than ten (10) days in advance of making a disclosure under this Section.

11. REPRESENTATIONS AND WARRANTIES

11.1 Mutual Representations and Warranties. Each Party represents and warrants to the other Party that, as of the Execution Date:

(a) it has the corporate power and authority to enter into this Agreement and to perform its obligations and bind its Affiliates to perform their obligations hereunder, and that the person(s) executing this Agreement on behalf of such Party are authorized to do so;

(b) the execution and delivery of this Agreement and the performance of the transactions contemplated hereunder have been duly authorized by all necessary corporate actions of such Party and its Affiliates;

(c) this Agreement has been duly executed and delivered by it and is a binding obligation of it, enforceable against it and its Affiliates in accordance with its terms; and

(d) the execution and delivery of this Agreement and the performance by such Party or its Affiliates of any of its obligations hereunder do not and will not conflict with (i) any judgment of any court or governmental body applicable to such Party or its Affiliates or its respective properties, (ii) any other agreements to which it or its Affiliates may be a party, or (iii) to such Party's knowledge, any statute, decree, order, rule or regulation of any court or governmental agency or body applicable to such Party, its Affiliates or their respective properties.

11.2 Additional Plaintiff Representations and Warranties. Plaintiffs represent and warrant to Defendants that they have the authority to grant rights under the Licensed Patents upon the terms set forth in this Agreement.

11.3 Disclaimer of Warranties. Except for those warranties set forth in Sections 3.3, 11.1 and 11.2, no Party makes any warranty, written, oral, express or implied, with respect to this Agreement. ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE AND NONINFRINGEMENT HEREBY ARE DISCLAIMED BY BOTH PARTIES.

12. INDEMNITIES.

12.1 Indemnity by Defendants. Defendants will, jointly and severally, indemnify and hold harmless Plaintiffs, their respective Affiliates and their or their respective Affiliates' officers, directors, employees and agents from and against any loss, damage, liability or expense in connection with any and all actions, suits, claims, demands or prosecutions that may be brought or instituted against Plaintiffs or such other indemnitees by Third Parties (including governmental authorities) to the extent based on or relating to (a) any breach by a Defendant of this Agreement; or (b) the manufacture, sale or offering to sell of any Zydus Generic Product, including any claim for personal injury, property damage, compensatory damages or punitive damages, provided that such claim does not arise out of or relate to the labeling of such Zydus Generic Product to the extent that, pursuant to applicable law, the label for such Zydus Generic Product must be the same as the label for the dosage-strength-equivalent Silenor Product.

12.2 Indemnity by Plaintiffs. Plaintiffs will, jointly and severally, indemnify and hold harmless Defendants, their respective Affiliates and their or their respective Affiliates' officers, directors, employees and agents from and against any loss, damage, liability or expense in connection with any and all actions, suits, claims, demands, or prosecutions that may be brought or instituted against Defendants or such other indemnitees by Third Parties (including governmental authorities) to the extent based on or relating to any breach by a Plaintiff of this Agreement.

12.3 Indemnification Procedures. A Person seeking indemnification under this Agreement shall provide prompt written notice to the indemnifying Party (and, in any event, within five (5) Business Days) of the assertion of any claim against such Party as to which indemnity is to be requested hereunder; provided, however, that any delay or failure to provide such notice shall not relieve the indemnifying Party of its indemnity obligations unless, and solely to the extent that, such delay or failure to notify prejudices the indemnifying Party's ability to defend such claims. The indemnifying Party shall have sole control over, and shall assume all expenses with respect to, the defense, settlement, adjustment or compromise of any claim as to which this Section 12 requires it to indemnify the other, provided that: (a) the indemnified Person may, if it so desires, employ counsel at its own expense to participate and assist in the handling of such claim; and (b) the indemnifying Party shall obtain the prior written approval of the indemnified Person, which shall not be unreasonably withheld, before entering into any settlement, adjustment or compromise of such claim or ceasing to defend against such claim if doing so would: (i) impose an injunction and/or any financial obligations upon the indemnified Person; or (ii) result in an admission of wrongdoing by the indemnified Person.

13. BREACH OF THE AGREEMENT

13.1 Each Party acknowledges and agrees that the restrictions and other terms and conditions set forth in this Agreement are reasonable and necessary to protect the respective legitimate interests of the Parties, and that, in the event of a material breach or threatened material breach of those restrictions or other terms or conditions of this Agreement by any Party, any other Party shall have the right to seek from any court of competent jurisdiction injunctive relief, whether temporary, preliminary, or permanent, or specific performance, which rights shall be cumulative and in addition to any other rights or remedies to which such other Party may be entitled in law or equity.

13.2 Nothing in this Agreement is intended, or shall be construed, to limit the Parties' rights to equitable relief or any other remedy for a breach of any provision of this Agreement. In the event of any breach by a Party described in this Section 13, each other Party reserves, and each Party so acknowledge, the right to seek damages, including enhanced damages, and other remedies for patent infringement to the full extent of the law.

13.3 Notwithstanding Sections 13.1 and 13.2, Plaintiffs hereby agree that their respective remedies in law and in equity relating to a Zydus At Risk Launch and sales of the Zydus Generic Product during the Zydus At Risk Period shall be limited to those set forth in Section 6 hereof.

14. GENERAL PROVISIONS

14.1 Entire Agreement. This Agreement (which includes Exhibit A attached hereto) constitute the final, complete and exclusive statement of the terms of the agreement among the Parties pertaining to the subject matter of this Agreement and supersedes all prior and contemporaneous understandings or agreements of the Parties. No Party has been induced to enter into this Agreement by, nor is any Party relying on, any representation or warranty outside those expressly set forth in this Agreement

14.2 Governing Law and Dispute Resolution. This Agreement shall be governed, interpreted and construed in accordance with the laws of the State of Delaware, without giving effect to choice of law principles. Any judicial proceedings related to disputes arising from or in connection with this Agreement shall be initiated exclusively in the District Court (or should there be no subject matter jurisdiction, then in another court of competent jurisdiction in Delaware), which shall be deemed to be the appropriate forum to hear the dispute.

14.3 Assignment. No Party will assign this Agreement or any part hereof or any interest herein (whether by operation of law or otherwise) to any Person without the written approval of the other Party; provided, however, that any Party may assign this Agreement without such consent (and, if Defendants so assigns this Agreement, they must assign the Zydus ANDA to the assignee of this Agreement, and Zydus shall not otherwise transfer or assign, or otherwise grant any Affiliate or Third Party any rights in, to or under the Zydus ANDA) (a) to any Affiliate of such assigning Party (for as long as such assignee remains an Affiliate of such Party); or (b) to any successor entity in the case of its merger, consolidation or change in control, or a sale of all or substantially all of its assets related to this Agreement. No assignment will be valid unless the permitted assignee assumes all obligations of its assignor under this Agreement. No assignment will relieve any assigning Party of responsibility for the performance of its obligations hereunder. Any purported assignment in violation of this Section 14.3 will be void.

14.4 Severability. Except as otherwise expressly provided herein, if any provision of this Agreement or the application thereof will, to any extent, be held to be invalid or unenforceable, then (a) the remainder of this Agreement, or the application of such provision to circumstances other than those as to which it is held invalid or unenforceable, will not be affected thereby and each provision of this Agreement will be valid and enforceable to the fullest extent permitted by applicable law, and (b) the Parties covenant and agree to renegotiate any such provision in good faith in order to provide a reasonably acceptable alternative to such provision, it being the intent of the Parties that the basic purposes of this Agreement are to be effectuated.

14.5 Independent Contractors. No Party shall be deemed to be an agent, joint venturer or partner of the other.

14.6 Amendments. No amendment, modification or supplement of any provisions of this Agreement shall be valid or effective unless made in writing and signed by a duly authorized officer of each Party.

14.7 Waiver. None of the provisions of this Agreement will be considered waived by any Party unless such waiver is agreed to, in writing, by authorized agents of such Party. The failure of a Party to insist upon strict conformance to any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law will not be deemed a waiver of any rights of any Party.

14.8 Counterparts and Facsimile Signatures. This Agreement may be executed simultaneously in several counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Signatures provided by facsimile transmission or in Adobe™ Portable Document Format (PDF) sent by electronic mail shall be deemed to be original signatures.

14.9 Construction.

(a) This Agreement has been jointly negotiated and drafted by the Parties through their respective counsel and no provision shall be construed or interpreted for or against any of the Parties on the basis that such provision, or any other provision, or the Agreement as a whole, was purportedly drafted by a particular Party.

(b) The word "including" or any variation thereof means "including without limitation" or any variation thereof and shall not be construed to limit any general statement which it follows to the specific or similar items or matters immediately following it.

(c) The section headings contained in this Agreement are inserted for convenience only and shall not affect in any way the meaning or interpretation of this Agreement.

14.10 Inurement. This Agreement shall be binding upon and inure solely to the benefit of the Parties, their successors and permitted assigns, and nothing in this Agreement, express or implied, is intended to or shall confer upon any other Person(s) (other than the Releasees under Section 3.1 and the indemnitees under Sections 12.1 and 12.2) any rights, benefits, or remedies of any nature whatsoever under or by reason of this Agreement.

14.11 Notices. Any notice required or permitted to be given or sent under this Agreement shall be in writing and hand delivered or sent by express delivery service or certified or registered mail, postage prepaid, to the receiving Party at the addresses indicated below.

If to Plaintiffs, to:

Somaxon Pharmaceuticals, Inc.
10935 Vista Sorrento Parkway, Suite 250
San Diego, CA 92130
Attn: General Counsel

And

ProCom One, Inc.
100 E. San Antonio, Ste 201
San Marcos TX 78666
Attn: President

with copies to:

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attn: David Manspeizer

If to Defendants, to:	Zydus Pharmaceuticals (USA), Inc. 73 Route 31 N. Pennington, NJ 08534 Attn: Executive Vice President and Head Global Intellectual Property
with copies to:	Locke Lord LLP 111 South Wacker Drive Chicago, IL 60606 Attn: Michael Gaertner

Any such notice shall be deemed to be effective on delivery, if delivery is confirmed by the delivery service. A Party may change its address by giving the other Parties written notice, delivered in accordance with this Section 14.11.

SIGNATURES FOLLOW ON NEXT PAGE

IN WITNESS WHEREOF, each of the Parties has caused this Agreement to be executed by its duly authorized representative as of the day and year first above written.

SOMAXON PHARMACEUTICALS, INC.

By: /s/ Richard W. Pascoe
Name: Richard W. Pascoe
Title: President and CEO

ZYDUS PHARMACEUTICALS (USA), INC.

By: /s/ Brij Khera
Name: Dr. Brij Khera
Title: Executive Vice President and Chief Legal Officer

PROCOM ONE, INC.

By: /s/ Terrell A. Cobb
Name: Terrell A. Cobb
Title: President

CADILA HEALTHCARE LIMITED

By: /s/ Pankaj Patel
Name: Pankaj Patel
Title: Chairman, Managing-Director

EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SOMAXON PHARMACEUTICALS, INC., and PROCOM ONE, INC.,	)	
Plaintiff,	)	
v.	)	**Civil Action No. 1:11-cv-00537-RGA**
ZYDUS PHARMACEUTICALS USA, INC., and CADILA HEALTHCARE LIMITED (d/b/a ZYDUS CADILA),	)	
Defendants.	)	

STIPULATION AND [PROPOSED] ORDER OF DISMISSAL

The Court, upon the consent and request of Plaintiffs Somaxon Pharmaceuticals, Inc. and ProCom One, Inc. (collectively, "Plaintiffs") and Defendants Zydus Pharmaceuticals (USA), Inc. and Cadila Healthcare Limited (collectively, "Defendants"), hereby acknowledges the following Stipulation and issues the following Order.

STIPULATION

Plaintiffs have charged Defendants with infringement of U.S. Patent Nos. 6,211,229 (the "'229 patent") and 7,915,307 (the "'307 patent") in connection with Zydus Pharmaceuticals (USA), Inc.'s submission to the U.S. Food and Drug Administration ("FDA") of Abbreviated New Drug Application ("ANDA") No. 202761 seeking approval to engage in the commercial manufacture, use, and/or sale of a 3 mg doxepin hydrochloride product and a 6 mg doxepin hydrochloride product (collectively, the "Zydus ANDA Products").

Defendants admit that the submission of ANDA No. 202761 to the FDA for the purpose of obtaining regulatory approval to engage in the commercial manufacture, use, and/or sale of the Zydus ANDA Products within the United States before the expiration of the '229 and '307 patents was an act of infringement of the '229 and '307 patents under 35 U.S.C. § 271(e)(2)(A).

Defendants admit that the commercial manufacture, use, offer for sale and/or sale of the Zydus ANDA Products within the United States, and/or the importation of such products into the United States, before the expiration of the '229 and '307 patents, other than in accordance with a license or other authorization from Plaintiffs, would infringe such patents.

Defendants admit that the '229 and '307 patents are valid and enforceable

The Parties agree that the remaining claims, counterclaims, and defenses in this action should be dismissed without prejudice.

ORDER

Accordingly, pursuant to the above Stipulation, and upon the consent and request of the Parties, **IT IS HEREBY ORDERED, ADJUDGED AND DECREED THAT**:

a) The parties' claims, counterclaims, and defenses with respect to the '229 and '307 patents are hereby dismissed without prejudice;

b) Defendants, their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them who receive actual notice of this Order by personal service or otherwise, are hereby enjoined from manufacturing, using, offering to sell and selling within the United States, and importing into the United States, the Zydus ANDA Products during the life of the '229 and '307 patents, including any extensions and pediatric exclusivities, absent a license or other authorization from Plaintiff, except to the extent permitted by the Settlement and License Agreement, and any subsidiary agreements, entered into between the parties, dated July , 2012.

c) This Stipulation And Order shall finally resolve the Action between the Parties, and the Parties each expressly waive any right to appeal or otherwise move for relief from this Stipulation And Order;

d) This Court retains jurisdiction over the Parties for purposes of enforcing this Stipulation and Order;

e) Each Party shall bear its own fees and costs in connection with the Action, including attorney fees;

[ ]

Attorneys for Plaintiffs Somaxon Pharmaceuticals, Inc. and ProCom One, Inc.

[ ]

Attorneys for Defendants Zydus Pharmaceuticals (USA), Inc. and Cadila Healthcare Limited

Dated: , 2012

SO ORDERED:

This day of , 2012.

HON. [ ]
UNITED STATES DISTRICT JUDGE

EXHIBIT C

EX-10.1 2 a17-10293_1ex10d1.htm EX-10.1

Exhibit 10.1

**CONFIDENTIAL MATERIALS OMITTED AND FILED
SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION.
ASTERISKS DENOTE OMISSIONS.**

EXECUTION COPY

SETTLEMENT AGREEMENT

BY AND BETWEEN

SUPERNUS PHARMACEUTICALS, INC.

AND

ZYDUS PHARMACEUTICAL (USA) INC.

CADILA HEALTHCARE LIMITED

DATED AS OF MARCH 6, 2017

THIS SETTLEMENT AGREEMENT, (this "**Settlement Agreement**") is entered into as of March 6, 2017 (the "**Effective Date**") by and between, Supernus Pharmaceuticals, Inc., a corporation organized and existing under the laws of Delaware, having offices located at 1550 East Gude Drive, Rockville, Maryland 20850 ("**Supernus**"), on the one hand, and Zydus Pharmaceutical (USA) Inc., a corporation organized and existing under the laws of New Jersey having offices located at 73 Route 31 N., Pennington, New Jersey 08534 ("**Zydus USA**") and Cadila Healthcare Limited, a corporation organized and existing under the laws of India, having offices located at Zydus Tower, Satellite Cross Roads, Ahmedabad-380015 Gujarat, India ("**Cadila**" and together with Zydus USA, "**Zydus**"), on the other hand. Supernus and Zydus are collectively referred to herein as the "**Parties**," or each individually as a "**Party**."

RECITALS:

WHEREAS, Supernus is the owner of New Drug Application No. 201635, which was approved by the Food and Drug Administration for the manufacture and sale of an extended release topiramate oral capsule product, which Supernus sells under the trade name Trokendi XR®;

WHEREAS, Zydus USA submitted Abbreviated New Drug Application No. 207382 (as defined in the License Agreement, the "**Zydus ANDA**") to the FDA under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (codified at 21 U.S.C. §355(j)) seeking approval to engage in the manufacture, use, sale, offer for sale, or importation of an extended release topiramate oral capsule product that is the subject of the Zydus ANDA (as defined in the License Agreement, the "**Zydus Product**");

WHEREAS, the filing of the Zydus ANDA included a "paragraph IV certification" seeking approval to engage in the manufacture, use and sale of the Zydus Product prior to the expiration of United States Patent Nos. 8,298,576 (the "**'576 Patent**"), 8,298,580 (the "**'580 Patent**"), 8,663,683 (the "**'683 Patent**"), 8,877,248 (the "**'248 patent**"), 8,889,191 (the "**'191 Patent**"), and 8,992,989 (the "**'989 Patent**," and together with the '576 Patent, the '580 Patent, the '683 Patent, the '248 Patent, and the '191 Patent, the "**Litigated Patents**");

WHEREAS, Supernus has prosecuted, and Zydus has defended, an action for patent infringement in the United States District Court for the District of New Jersey (the "Court") regarding the Zydus ANDA and the Zydus Product, which action is captioned *Supernus Pharmaceuticals, Inc. v. Zydus Pharmaceutical (USA) Inc., et. al.*, (Civil Action No. 2:14-cv-07272-SDW-SCM) (the "Pending Litigation");

WHEREAS, Supernus and Zydus wish to settle the Pending Litigation and have reached an agreement, encompassing the terms and conditions set forth in this Settlement Agreement together with a License Agreement (the "**License Agreement**," attached hereto as Exhibit A) and an agreed Stipulation of Dismissal with regard to the Pending Litigation (the "**Dismissal**," attached hereto as Exhibit B) (with the Settlement Agreement, the License Agreement, and the Dismissal being collectively referred to as the "**Settlement Documents**");

WHEREAS, neither Supernus nor Zydus have received any consideration from the other for their entry into this Settlement Agreement other than that which is set forth in the Settlement Documents; and

WHEREAS, the Settlement Documents constitute Zydus's and Supernus' best independent judgment as to the most convenient, effective and expeditious way to mutually settle all disputes that have arisen associated with the Zydus ANDA.

NOW, THEREFORE, in consideration of the mutual covenants and agreements described herein, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

1. Capitalized terms used, but not defined herein, shall have the meanings ascribed to them in the License Agreement.

2. The Parties consent to the jurisdiction of the Court for the purposes of the settlement of the Pending Litigation.

3. The Parties agree that the Court has jurisdiction over the Pending Litigation and over Supernus and Zydus, and that venue is proper in the District of New Jersey.

4. Zydus admits, solely with respect to the Zydus ANDA and the Zydus Product, that the Litigated Patents, and all the claims contained therein, are valid and enforceable.

5. Zydus admits, solely with respect to the Zydus ANDA and the Zydus Product, that the claims of the Litigated Patents asserted as of the Effective Date in the Pending Litigation, were infringed by the filing of the Zydus ANDA and, absent a license from Supernus, would be infringed by the manufacture, use, sale, offer for sale, or importation of the Zydus Product in the Territory.

6. Notwithstanding the foregoing, the parties agree that nothing prohibits Zydus from asserting any and all counterclaims or defenses of invalidity, non-infringement or unenforceability in view of the Litigated Patents in any proceeding the subject matter of which is not the Zydus Product or a Generic Equivalent Product (and may file a petition for ex parte reexamination, Inter Partes Review (IPR), and Post Grant Review (PGR) of a Litigated Patent, if such Litigated Patent is asserted against Zydus or its Affiliates in any proceeding the subject matter of which is not the Zydus Product or a Generic Equivalent Product).

7. Supernus represents, warrants, and covenants that Supernus is the sole owner of the Litigated Patents, and Supernus possesses the sole right to enforce the Litigated Patents.

8. Zydus represents, warrants, and covenants that it has not granted or assigned to any Third Party, directly or indirectly, any right or license under or to the Zydus ANDA or the Zydus Product, and that it will not, except in accordance with the License Agreement, do any of the foregoing (including, selling, assigning, transferring, or divesting the Zydus ANDA to a Third Party).

9. In consideration of the mutual execution of the Settlement Documents and the mutual agreement to be legally bound by the terms hereof, each of Supernus and Zydus, with the intention of binding itself and its Affiliates and its and their respective predecessors, successors, heirs and assigns, directors, officers, employees and representatives, hereby fully, finally and irrevocably release and discharge the other Party, and its Affiliates and its and their respective directors, officers, employees, customers, importers, manufacturers, distributors, suppliers, insurers, attorneys, representatives and agents, or any heirs, administrators, executors, predecessors, successors, or assigns of the foregoing, from any and all actions, causes of action, suits, debts, dues, sums of money, accounts, reckonings, bonds, bills, specialties, covenants, contracts, liabilities, controversies, agreements, promises, variances, trespasses, damages, judgments, extents, executions, claims, counterclaims, demands, costs, expenses, losses, liens and obligations, whatsoever, in law or equity, whether known or unknown, pending or future, certain or contingent, occurring before or as of the Effective Date related to the Litigated Patents, including (i) in connection with the Pending Litigation, (ii) associated with the Zydus ANDA and Zydus Product, and including Supernus' assertion of the Litigated Patents against Zydus, or (iii) all other claims that were asserted or could have been asserted in the Pending Litigation (collectively, the "**Released Claims**"). For purposes of clarity, nothing herein shall inhibit any Party's ability to enforce the terms of the Settlement Documents, or Supernus' ability to enforce any patent, including the Litigated Patents against Third Parties, or Zydus's ability to assert counterclaims or defenses of non-infringement, invalidity, or unenforceability of the Litigated Patents in any proceeding the subject matter of which is not the Zydus Product. EACH PARTY ACKNOWLEDGES THAT IT MAY HEREAFTER DISCOVER CLAIMS OR FACTS IN ADDITION TO OR DIFFERENT FROM THOSE WHICH IT NOW KNOWS OR BELIEVES TO EXIST WITH RESPECT TO THE RELEASED CLAIMS, THE FACTS AND CIRCUMSTANCES ALLEGED IN THE ACTION, AND/OR THE SUBJECT MATTER OF THIS SETTLEMENT AGREEMENT, WHICH, IF KNOWN OR SUSPECTED AT THE TIME OF EXECUTING THIS SETTLEMENT AGREEMENT, MAY HAVE MATERIALLY AFFECTED THIS SETTLEMENT AGREEMENT. NEVERTHELESS, UPON THE EFFECTIVENESS OF THE RELEASE OF THE RELEASED CLAIMS AS SET FORTH IN THIS SECTION, EACH PARTY HEREBY ACKNOWLEDGES THAT THE RELEASED CLAIMS INCLUDE WAIVERS OF ANY RIGHTS, CLAIMS, OR CAUSES OF ACTION THAT MIGHT ARISE AS A RESULT OF SUCH DIFFERENT OR ADDITIONAL CLAIMS OR FACTS. EACH PARTY ACKNOWLEDGES THAT IT UNDERSTANDS THE SIGNIFICANCE AND POTENTIAL CONSEQUENCES OF SUCH A RELEASE OF UNKNOWN UNITED STATES JURISDICTION CLAIMS AND OF SUCH A SPECIFIC WAIVER OF RIGHTS. EACH PARTY INTENDS THAT THE CLAIMS RELEASED BY IT UNDER THIS RELEASE BE CONSTRUED AS BROADLY AS POSSIBLE TO THE EXTENT THEY RELATE TO UNITED STATES JURISDICTION CLAIMS. ZYDUS IS AWARE OF CALIFORNIA CIVIL CODE SECTION 1542, WHICH PROVIDES AS FOLLOWS:

> "A general release does not extend to claims which the creditor does not know or suspect to exist in his or her favor at the time of executing the release, which if known by him or her, must have materially affected his or her settlement with the debtor."

EACH PARTY AGREES TO EXPRESSLY WAIVE ANY RIGHTS IT MAY HAVE UNDER THIS CODE SECTION OR UNDER FEDERAL, STATE, OR COMMON LAW STATUTES OR JUDICIAL DECISIONS OF A SIMILAR NATURE, AND KNOWINGLY AND VOLUNTARILY WAIVES ALL SUCH UNKNOWN RELEASED CLAIMS.

10. Supernus and Zydus each represents and warrants that it has the full right, authority and power to enter into the Settlement Documents on its own behalf, and on behalf of its Affiliates, and that the Settlement Documents shall create and constitute a binding obligation on its part as of the Effective Date.

11. Supernus and Zydus agree that each will bear its own costs and legal fees for the Pending Litigation.

12. From the execution of the Settlement Documents, and unless the Settlement Documents are terminated, neither Party will actively pursue litigation activities related to the Pending Litigation, except to the extent required by court order or other Applicable Law. In consideration of the benefits of entering into the Settlement Documents, the Parties, through their respective attorneys, shall, within two (2) Business Days of the Effective Date, jointly seek that the Court enter the Dismissal. In the event that the Court should refuse to enter the Dismissal, the Parties shall work together in good faith to modify the Dismissal to meet the Court's requirements, provided that nothing contained herein shall be deemed to require a Party to agree to a modification of the Dismissal or any other Settlement Document that materially affects the economic value of the transactions contemplated hereby. If despite such good faith efforts the Court refuses within thirty (30) days of the Effective Date to enter the Dismissal, the Settlement Documents shall be null and void *ab initio*.

13. The Parties shall submit the Settlement Documents to the Federal Trade Commission Bureau of Competition (the "**Commission**") and the Assistant Attorney General in charge of the Antitrust Division of the Department of Justice (the "**DOJ**") as soon as practicable following the Effective Date and in no event later than ten (10) Business Days following the Effective Date. The Parties shall use all reasonable efforts to coordinate the making of such filings, and shall respond promptly to any requests for additional information made by either of such agencies. Each Party reserves the right to communicate with the Commission or the DOJ regarding such filings as it believes appropriate. Each Party shall keep the other reasonably informed of such communications and shall not disclose the Confidential Information of the other without such other Party's consent (not to be unreasonably withheld). To the extent that any legal or regulatory issues or barriers arise with respect to the Settlement Documents, or any subpart thereof, the Parties shall work together in good faith and use reasonable efforts to modify the Settlement Documents to overcome any such legal or regulatory issues (including, for example, objections by the Commission, the DOJ or any applicable court) in a mutually acceptable fashion, but in no event shall either Party be required to agree to any modification of the Settlement Documents that materially affects the economic value of the transactions contemplated hereby. For purposes of this Settlement Agreement, "reasonable efforts" shall mean reasonable efforts and commitment of resources consistent with such Party's similarly situated products or projects in order to achieve a stated goal as expeditiously as practical.

14. This Settlement Agreement shall terminate upon the expiration of the Litigated Patents and any statutory or regulatory extensions, provided that Section 9 of this Settlement Agreement shall survive any such termination.

15. The Settlement Documents are governed under the provisions of the following Sections of the License Agreement: 5 (Confidentiality); 11.1 and 11.2 (Notice); 11.3 (Assignment); 11.4 (Amendment); 11.5 (Public Announcement); 11.6 (Merger and Integration); 11.7 (Governing Law); 11.8 (Agreement Costs); 11.9 (Counterparts); 11.10 (Severability); 11.11 (Relationship of the Parties); 11.12 (Construction); 11.13 (Dispute Resolution); 11.14 (Cumulative Rights); 11.15 (No Third Party Benefit); 11.16 (Further Assurance); and 11.17 (Waiver).

[Signature Page Follows]

[Signature Page to
Settlement Agreement Regarding Extended Release Topiramate Oral Capsule Product]

IN WITNESS WHEREOF, the Parties hereto have each caused this Settlement Agreement to be executed by their authorized representatives as of the Effective Date.

SUPERNUS PHARMACEUTICALS, INC.

By: /s/ Jack Khattar

Name: Jack Khattar

Title: President & CEO

ZYDUS PHARMACEUTICAL (USA) INC.

By: _____

Name: _____

Title: _____

CADILA HEALTHCARE LIMITED

By: _____

Name: _____

Title: _____

[Signature Page to
Settlement Agreement Regarding Extended Release Topiramate Oral Capsule Product]

IN WITNESS WHEREOF, the Parties hereto have each caused this Settlement Agreement to be executed by their authorized representatives as of the Effective Date.

SUPERNUS PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____

ZYDUS PHARMACEUTICAL (USA) INC.

By: /s/ Brij Khera

Name: Brij Khera

Title: Executive Vice President &
Chief Legal Officer

CADILA HEALTHCARE LIMITED

By: /s/ Pankaj Patel

Name: Pankaj Patel

Title: Chairman & Managing Director

EXHIBIT A

LICENSE AGREEMENT

BY AND BETWEEN

SUPERNUS PHARMACEUTICALS, INC.

AND

ZYDUS PHARMACEUTICAL (USA) INC.

CADILA HEALTHCARE LIMITED

DATED AS OF MARCH 6, 2017

LICENSE AGREEMENT

THIS LICENSE AGREEMENT (this "**License Agreement**") is entered into as of March 6, 2017 (the "**Effective Date**") by and between, Supernus Pharmaceuticals, Inc., a corporation organized and existing under the laws of Delaware, having offices located at 1550 East Gude Drive, Rockville, Maryland 20850, ("**Supernus**"), on the one hand, and Zydus Pharmaceutical (USA) Inc., a corporation organized and existing under the laws of New Jersey having offices located at 73 Route 31 N., Pennington, New Jersey 08534 ("**Zydus USA**") and Cadila Healthcare Limited, a corporation organized and existing under the laws of India, having offices located at Zydus Tower, Satellite Cross Roads, Ahmedabad-380015 Gujarat, India ("**Cadila**" and together with Zydus USA, "**Zydus**"), on the other hand. Supernus and Zydus are collectively referred to herein as the "**Parties**," or each individually as a "**Party**."

R E C I T A L S:

WHEREAS, Supernus and Zydus are parties to a certain Settlement Agreement of even date herewith (the "**Settlement Agreement**"), pursuant to which Supernus and Zydus are settling the Pending Litigation; and

WHEREAS, in accordance with the Settlement Agreement, Supernus and Zydus have agreed to enter into this License Agreement as part of the Settlement Documents (as defined in the Settlement Agreement, the "**Settlement Documents**").

NOW THEREFORE, in consideration of the foregoing premises, the mutual covenants and agreements described herein and in the Settlement Agreement, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

1. Definitions.

1.1 "Accelerated License Date" means the earlier of: (i) the date of a ** all the ** of the ** and ** a ** with respect to a ** to be **; (ii) the date of the ** of a ** following a ** all the ** of the ** and ** the ** to be **, ** or ** by such **; (iii) the date an ** may be ** by a **, whether pursuant to a **, **, ** or other ** Supernus and a **; (iv) the date of the ** of ** by Supernus or its Affiliates; (v) the date an ** may be ** by any **; or (vi) the date all the ** are ** from the ** for the Trokendi XR Product.

1.2 "Affiliate" means, with respect to a Party, a Person that controls, is controlled by or is under common control with such Party. For the purposes of this definition, the word "control" (including, with correlative meaning, the terms "controlled by" or "under common control with") means the actual power, either directly or indirectly through one or more intermediaries, to direct the management and policies of such Person, whether by the ownership of fifty percent (50%) or more of the voting interest of such Person (it being understood that the direct or indirect ownership of a lesser percentage of such interest shall not necessarily preclude the existence of control), or by contract or otherwise.

** This portion has been redacted pursuant to a confidential treatment request.

1.3 **"AG Product"** means a product that is not Labeled with the Trokendi XR® trademark containing the Compound as its sole active ingredient that is Marketed or supplied under the Supernus NDA, described therein now or hereafter.

1.4 **"ANDA"** means an Abbreviated New Drug Application to the FDA for approval to Manufacture and Market a pharmaceutical product in or into the Territory.

1.5 **"Anticipated License Date"** means January 1, 2023.

1.6 **"Applicable Law"** means the applicable Laws, rules, regulations, guidelines and requirements of any Governmental Authority related to the performance of either Party's obligations under the Settlement Documents.

1.7 **"At-Risk Launch"** means the First Commercial Sale of a Generic Equivalent Product, other than an Authorized Generic ANDA Product, by a Third Party, other than a Third Party acting pursuant to an agreement or understanding or otherwise in privity with Zydus or its Affiliates, preceding a Final Court Decision holding all the claims of the Litigated Patents asserted and finally adjudicated against the Third Party to be invalid, unenforceable or not infringed by such Generic Equivalent Product.

1.8 **"At-Risk Launch Date"** means the date of the First Commercial Sale for an At-Risk Launch.

1.9 **"At-Risk License Date"** means (i) if ** a **, the ** of (x) ** the **, (y) if the ** was ** in an **, the date the ** the **, and (z) if the ** was ** in a ** and the ** the ** of (a) ** after the date the ** the **, and (b) if ** a ** in an **, the date the ** the **; and (ii) if ** does not ** with the ** a **, ** the **; provided, in each case, that the ** which is the subject of the ** continues to be ** in the ** on such date.

1.10 **"At-Risk Period"** shall have the meaning assigned to such term in the Section 4.3.5.

1.11 **"Authorized Generic ANDA Product"** means a ** authorized, whether pursuant to a ** or **, for Marketing pursuant to an agreement between Supernus and a Third Party. For the avoidance of doubt, if Supernus enters into an agreement with a Third Party that ** the ** of a ** in the Territory, and such agreement includes a **, **, **, ** or the like with respect to ** of such **, such ** shall not be considered an ** by virtue of such ** or the like, provided such ** is no longer being Marketed in the Territory.

1.12 **"Business Day"** means any day other than a Saturday, Sunday or a day on which banks in New York, New York are authorized or required by Law to close.

1.13 **"Claim"** means any Third Party claim, lawsuit, investigation, proceeding, regulatory action or other cause of action.

** This portion has been redacted pursuant to a confidential treatment request.

1.14 **"Commercially Reasonable Efforts"** means efforts and diligence in accordance with Zydus's reasonable and sound business, legal, medical and scientific judgment and in accordance with the efforts and resources Zydus would use in other aspects of its business that have similar commercial value and market potential, taking into account the competitiveness of the marketplace, the business life-cycle, the proprietary position of Zydus and the profitability of the pertinent product.

1.15 **"Compound"** means topiramate.

1.16 **"Confidential Information"** means, subject to Section 5.1, any scientific, technical, formulation, process, Manufacturing, clinical, non-clinical, regulatory, Marketing, financial or commercial information or data relating to the business, projects, employees or products of either Party and provided by one Party to the other by written, oral, electronic or other means in connection with the Settlement Documents.

1.17 **"Covenant Not to Sue"** shall have the meaning assigned to such term in Section 3.5.

1.18 **"Effective Date"** shall have the meaning assigned to such term in the preamble to this License Agreement.

1.19 **"FDA"** means the United States Food and Drug Administration or any successor agency thereof.

1.20 **"Final Court Decision"** means a final decision of any Federal court from which no appeal has been taken or can be taken within the time permitted therefor (other than a petition to the United States Supreme Court for a *writ of certiorari*).

1.21 **"First Commercial Sale"** means the Shipment by a Third Party of commercial quantities of product for immediate commercial sale in the Territory to retail chains, pharmaceutical wholesalers, health care providers, or managed care providers in the Territory. In the event that Zydus provides written notice to Supernus advising that Zydus has determined that a Third Party has completed the First Commercial Sale of a Generic Equivalent Product and the date of such First Commercial Sale (a "**Safe Harbor Notice**"), and Supernus confirms such determination or fails to deliver written notice to Zydus reasonably and in good faith objecting to such determination (and setting forth independent and reliable information gained from reliable sources in the trade) within ** after receipt of such Safe Harbor Notice from Zydus, then a First Commercial Sale shall be conclusively deemed to have occurred on such date. In the event that Supernus delivers timely written notice to Zydus reasonably and in good faith objecting to the determination (and setting forth independent and reliable information gained from reliable sources in the trade) set forth in the Safe Harbor Notice, Supernus shall be deemed to have reserved its right to dispute the occurrence of the First Commercial Sale.

1.22 **"**"** shall have the meaning assigned to such term in **.

** This portion has been redacted pursuant to a confidential treatment request.

1.23 **"Force Majeure"** means any circumstances reasonably beyond a Party's control, including, acts of God, civil disorders or commotions, acts of aggression, terrorism, fire, explosions, floods, drought, war, sabotage, embargo, utility failures, supplier failures, material shortages, labor disturbances, a national health emergency, or appropriations of property.

1.24 **"GAAP"** means generally accepted accounting principles in effect in the United States from time to time, consistently applied.

1.25 **"Generic Equivalent Product"** means an extended release oral capsule product containing the Compound as its sole active ingredient which is submitted to the FDA for Regulatory Approval pursuant to an ANDA or 505(b)(2) application as a Therapeutic Equivalent to the Trokendi XR Product. For clarity, Generic Equivalent Product shall not include AG Product.

1.26 **"Governmental Authority"** means any court, tribunal, arbitrator, agency, legislative body, commission, official or other instrumentality of: (i) any government of any country; or (ii) a federal, state, province, county, city or other political subdivision thereof.

1.27 **"Label"** means any Package labeling designed for use with a product, including the package insert for such product that is approved by the FDA, and "**Labeled**" or "**Labeling**" shall have the correlated meaning.

1.28 **"Launch"** means the first Shipment of a Generic Equivalent Product to a Third Party.

1.29 **"Law"** or **"Laws"** means all laws, statutes, rules, codes, regulations, orders, judgments and ordinances of any Governmental Authority.

1.30 **"License and Authorization"** shall have the meaning assigned to such term in Section 2.2.

1.31 **"Licensed Patents"** means: (i) the Litigated Patents and any patent that issues as a result of a continuation, continuation-in-part, divisional, reexamination or reissue thereof; and (ii) any other present or future U.S., international, or foreign patent owned or controlled by Supernus or any of its Affiliates which claims cover the Manufacturing, Marketing, Shipping, using, or importing of the Zydus Product.

1.32 **"Litigated Patents"** shall have the meaning assigned to such term in the Settlement Agreement.

1.33 **"Losses"** means any liabilities, damages, costs or expenses, including reasonable attorneys' fees and expert fees, incurred by any Party that arises from any claim, lawsuit or other action by a Third Party.

1.34 **"Manufacture"** means all activities related to the manufacturing, development and use of a pharmaceutical product, or any ingredient thereof, including, manufacturing Compound or supplies for development, manufacturing a product for commercial sale, packaging, in-process and finished product testing, release of product or any component or

ingredient thereof, quality assurance activities related to manufacturing and release of product, ongoing stability tests and regulatory activities related to any of the foregoing, and **"Manufactured"** or **"Manufacturing"** shall have the correlated meaning.

1.35 **"Market"** means to distribute, promote, advertise, market, offer for sale or sell, to a Third Party, and **"Marketing"** or **"Marketed"** shall have the correlated meaning.

1.36 **"Net Sales"** shall equal the ** for sales of the Zydus Product to Third Parties in the Territory ** all **, all as determined in accordance with ** for other pharmaceutical products and consistent with the customary practices in the generic pharmaceutical industry in the Territory, **, and which, as applicable, are actually **, **, ** or specifically **, including:

1.36.1 **, **, **, **, ** or other **;

1.36.2 ** and **, ** and any other ** or ** and **, ** and ** (including **), all to the extent ** to the ** and ** and ** in accordance with applicable Law (but ** the ** from such **);

1.36.3 **, ** and **, ** and **;

1.36.4 **, including ** (including those on ** following price changes) and ** for ** or **;

1.36.5 **, **, **, any other ** (including **, ** and **) actually ** or ** to any Person, including **, ** and to **, including their **, or to **, in each case that are not Affiliates of Zydus, and that are directly attributable to the sale of the Zydus Product;

1.36.6 ** and similar payments made with respect to ** for by ** or **, ** or similar ** in the Territory (including ** and ** program **, ** and ** for ** required by the ** and **); and

1.36.7 **, and like ** that are customary in the industry that are ** from **, and other ** to **.

For the sake of clarity, all such deductions represent reductions to the ** for sales of the Zydus Product by Zydus or its Affiliates to Third Parties in the Territory in accordance with GAAP.

1.37 **"NDA"** means a New Drug Application (or equivalent regulatory mechanism) filed with the FDA pursuant to and under 21 U.S.C. § 355(b) (as amended, supplemented or replaced), together with the FDA's implementing rules and regulations.

1.38 **"Orange Book"** means the "Approved Drug Products with Therapeutic Equivalence Evaluations" published by FDA.

** This portion has been redacted pursuant to a confidential treatment request.

1.39 **"Package"** means all primary containers, including bottles, cartons, shipping cases or any other like matter used in packaging or accompanying a product, and "Packaged" or "Packaging" shall have the correlated meaning.

1.40 **"Party"** or **"Parties"** shall have the meaning assigned to such term in the preamble to this License Agreement.

1.41 **"Pending Litigation"** shall have the meaning assigned to such term in the Settlement Agreement.

1.42 **"Person"** means any individual, partnership, association, corporation, limited liability company, trust, or other legal person or entity.

1.43 **"Regulatory Approval"** means final Marketing approval by the FDA for the Marketing of a pharmaceutical product in the Territory.

1.44 **"Settlement Agreement"** shall have the meaning assigned to such term in the Recitals.

1.45 **"Shipped"** means, with respect to a product, when a Person has delivered shipments of such product to a common carrier in the Territory for shipment to other Persons for resale; in each instance, **"Shipment," "Ship"** or **"Shipping"** shall have the correlated meaning.

1.46 **"Supernus"** shall have the meaning assigned to such term in the preamble to this License Agreement.

1.47 **"Supernus NDA"** means NDA No. 201635, as amended, or supplemented.

1.48 **"Supernus Party"** shall have the meaning assigned to such term in Section 7.2.

1.49 **"Supernus' External Auditor"** shall have the meaning assigned to such term in Section 4.8.

1.50 **"Term"** shall have the meaning assigned to such term in Section 10.1.

1.51 **"Territory"** means the United States of America, and its territories, commonwealths, districts and possessions, including the Commonwealth of Puerto Rico.

1.52 **"Therapeutic Equivalent"** shall have the meaning given to it by the FDA in the current edition of the Orange Book as may be amended from time to time during the Term.

1.53 **"Third Party"** or **"Third Parties"** means any Person or entity other than a Party or its Affiliates.

1.54 **"Third Party Agreement"** shall have the meaning assigned to such term in Section 3.8.

1.55 **"Trokendi XR Product"** means the extended release oral capsule product containing the Compound as its sole active ingredient which is approved for Marketing pursuant to the Supernus NDA and is Marketed in the Territory under the Trokendi XR® trademark (or a successor trademark adopted for such product).

1.56 **"TRO/PI"** means a motion for temporary restraining order and/or preliminary injunction, or other court filing, in each case seeking cessation or prevention of an At-Risk Launch.

1.57 **"Zydus"** shall have the meaning assigned to such term in the preamble to this License Agreement.

1.58 **"Zydus ANDA"** shall mean ANDA No. 207382 (together with any amendments, supplements, or other changes thereto) seeking approval to engage in the Manufacture, use and sale of an extended release oral capsule product containing the Compound as its sole active ingredient.

1.59 **"Zydus Launch"** means a Launch by Zydus of a Zydus Product.

1.60 **"Zydus License Date"** means the ** of:

1.60.1 the **;

1.60.2 an **; or

1.60.3 an **.

1.61 **"Zydus Party"** shall have the meaning assigned to such term in Section 7.1.

1.62 **"Zydus Product"** means an extended release oral capsule product containing the Compound as its sole active ingredient, which is the subject of the Zydus ANDA, including all formulations and strengths thereof, described therein now or hereafter.

2. **License and Authorization**

2.1 Subject to the terms, conditions and limitations hereof, including the conditions set forth in Section 3, Supernus hereby grants to Zydus a non-exclusive license, under the Licensed Patents to: (i) Manufacture, have Manufactured, import, use and Market the Zydus Product in, into or for the Territory, on and after the applicable Zydus License Date; and (ii) Manufacture, and have Manufactured, import and conduct regulatory activities regarding the Zydus Product in, into or for the Territory prior to the Zydus License Date (but not to Market or Ship the Zydus Product prior to the Zydus License Date) in sufficient quantities to permit Zydus to Market and Ship the Zydus Product in, into or for the Territory beginning ** prior to the Zydus License Date, (iii) beginning ** prior to a date in good faith anticipated by Zydus to be the date

** This portion has been redacted pursuant to a confidential treatment request.

that a Final Court Decision will be entered finding all the claims of the Litigated Patents asserted and finally adjudicated against a Third Party with respect to a Generic Equivalent Product to be invalid, unenforceable or not infringed by such Generic Equivalent Product (a **"Potential Final Court Decision"**), Manufacture, and have Manufactured, import and conduct regulatory activities regarding the Zydus Product in, into or for the Territory prior to the Zydus License Date (but not to Market or Ship the Zydus Product prior to the Zydus License Date) in sufficient quantities to permit Zydus to Market and Ship the Zydus Product in, into or for the Territory on and after the Zydus License Date; provided that all Zydus Product remain at Zydus' or its distributor's warehouse until a Zydus License Date; and further provided, that Zydus shall re-export (or, at Zydus' option, destroy) any Zydus Product which remains in the Territory at such time that Zydus in good faith determines that no such Final Court Decision will be issued with respect to a Third Party's Generic Equivalent Product and no Accelerated License Date will result from such Potential Final Court Decision. To the extent Supernus owns or controls any regulatory exclusivities granted by the FDA that may prevent or hinder Regulatory Approval or Marketing of the Zydus Product, Supernus hereby waives, effective as of the date that Zydus is licensed to conduct the applicable activity hereunder, such exclusivities. Supernus shall, if requested by Zydus, send the FDA a written confirmation of Supernus' grant of the foregoing license under the Licensed Patents and Supernus' agreement to waive, effective as of the date that Zydus is licensed to conduct the applicable activity hereunder, such regulatory exclusivities with respect to the Zydus Product or the Zydus ANDA.

2.2 The license and authorization granted in Section 2.1 and Section 3.1 of this License Agreement are referred to herein as the "License and Authorization." Except to the extent permitted pursuant to Section 11.3, and without derogating from Zydus's "have Manufactured" rights set forth in Section 2.1, Zydus and its Affiliates shall not have the right to sublicense, assign or transfer any of its rights under the License and Authorization.

2.3 In the event the ** becomes effective due to an ** and there are thereafter no longer any ** the ** in the ** (other than ** or ** subject to substantially the same provisions as set forth in this Section), ** from **, ** to ** under the ** shall immediately terminate, and ** and its ** shall ** (no ** than the ** of the ** following Zydus' receipt of such notice) the ** and ** of ** until such subsequent ** as another event constituting a ** shall have occurred.

2.4 Except as set forth in the License and Authorization or expressly set forth in this License Agreement or other Settlement Documents, there are no authorizations, licenses or rights granted by either Party under this License Agreement, by implication, estoppel or otherwise, including any right granted to Zydus or its Affiliates to Market or Manufacture any Generic Equivalent Product except under the Zydus ANDA. All rights not expressly granted by Supernus herein are hereby retained by Supernus. In addition, except as expressly set forth in this License Agreement or other Settlement Documents, Supernus explicitly retains the right itself or through an Affiliate to Market an AG Product, and Supernus is free to grant a license under the Licensed Patents or supply AG Product to any Third Party.

2.5 ** shall ** to ** (i.e., ** shall be **) as ** to the **.

** This portion has been redacted pursuant to a confidential treatment request.

3. Covenants

3.1 Except as expressly provided in Section 2.1, Zydus and its Affiliates hereby agree not to manufacture, have manufactured, import, sell, offer to sell or use Zydus Product in the Territory prior to the applicable Zydus License Date. Notwithstanding the foregoing and in addition to Section 2.1, Supernus hereby grants Zydus a limited license, commencing ** days prior to the Zydus License Date, to communicate to potential purchasers that Zydus will be selling the Zydus Product in the Territory on or after the Zydus License Date (including, for example, notification to customers regarding the Zydus Product, and engaging customers in non-binding pricing/contracting activities), and shipping or delivering or distributing the Zydus Product to Third Party distributors or Affiliated distributors, in each case solely for the purpose of conducting preparations for a Zydus Launch in or into the Territory on the Zydus License Date.

3.2 Zydus shall not assist, coordinate with, or otherwise help any Third Parties in prosecuting, defending, or settling their litigations concerning their ANDA to Market any Generic Equivalent Product, except as required by Law. Zydus and its Affiliates hereby agree not to: (i) challenge the validity or enforceability of the Litigated Patents (including but not limited to a petition for ex parte reexamination, Inter Partes Review (IPR), and Post Grant Review (PGR)); (ii) aid, abet, assist, enable or participate with any Third Party in a challenge to the validity or enforceability of the Litigated Patents or the non-infringement of a Generic Equivalent Product; (iii) Market or Manufacture a Generic Equivalent Product other than the Zydus Product pursuant to the License and Authorization; or (iv) aid, abet, enable or contract with any Third Party regarding the Marketing or Manufacturing of any Generic Equivalent Product in or into the Territory other than the Zydus Product. Notwithstanding the foregoing, nothing herein shall prohibit Zydus from asserting any and all counterclaims or defenses of invalidity, non-infringement or unenforceability in view of the Litigated Patents in any proceeding the subject matter of which is not the Zydus Product or a Generic Equivalent Product (and may file a petition for ex parte reexamination, Inter Partes Review (IPR), and Post Grant Review (PGR) of a Litigated Patent, if such Litigated Patent is asserted against Zydus or its Affiliates in any proceeding the subject matter of which is not the Zydus Product or a Generic Equivalent Product).

3.3 In addition to any other right or remedy Supernus may be entitled to, in the event that Zydus or its Affiliates breaches Sections 3.1 or 3.2, Supernus may, at its sole discretion, immediately, effective upon notice to Zydus, terminate all, or any of, the License Agreement or the Settlement Agreement.

3.4 Nothing set forth herein or in the other Settlement Documents shall be deemed to give Supernus any control over any Marketing exclusivity that may be granted to Zydus by the FDA in connection with the Zydus ANDA or the Zydus Product. Nothing set forth herein or in the other Settlement Documents shall be deemed to prevent or restrict Zydus from Manufacturing or Marketing any Generic Equivalent Product which would not infringe the Licensed Patents, and nothing herein shall prohibit Zydus from entering into any agreement with

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a Third Party related to any Generic Equivalent Product that does not infringe the Licensed Patents.

3.5 Supernus hereby covenants not to sue Zydus or its Affiliates or any of their respective shareholders, licensees, sublicensees, customers, suppliers, importers, manufacturers, distributors, insurers, or any heirs, administrators, executors, predecessors, successors, or assigns of the foregoing, or cause or authorize any Person to do any of the foregoing, claiming or otherwise asserting that the manufacture, use, sale, offer for sale, or importation of the Zydus Product infringes the Licensed Patents (the "**Covenant Not to Sue**"). Supernus will impose the foregoing Covenant Not to Sue on any Third Party to which Supernus may assign, grant a right to enforce, or otherwise transfer (by any means) any of the Licensed Patents subject to the foregoing Covenant Not to Sue. The Covenant Not to Sue shall not apply in the event Supernus has terminated this License Agreement. For any of the Licensed Patents listed in the Orange Book for the Trokendi XR Product, the Covenant Not to Sue will hereby be treated as a non-exclusive license, so that Zydus or its Affiliates may file and maintain with the FDA "Paragraph IV Certifications" under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (as amended or replaced) and 21 U.S.C. § 355(b)(2)(A)(iv) (as amended or replaced) with respect to the Zydus ANDA.

3.6 Supernus and its affiliates shall not ** to ** with the FDA approval of the Zydus ANDA, or the ** of the ** as of the Zydus License Date, including by: (i) **, **, ** as "**" or ** the ** prior to the ** after the ** of the ** in the **; (ii) ** or ** any ** with respect to the ** from the **; (iii) ** for the **; (iv) **, **, ** to **, or otherwise ** the ** of the ** (** due to a ** or ** issue based on **, **) prior to the ** of the ** in the **; (v) ** or otherwise ** any ** with the ** to ** any of the ** from the ** (** due to a ** or ** issue based on **, **) prior to the ** after ** of the ** in the **; or (vi) filing any ** with the ** relating to ** which ** the ** of the **, ** for purposes of ** or ** which are based on **, **.

3.7 Zydus covenants that Zydus and its Affiliates will not grant a written release of any right, or grant a written waiver of conflict of interest, in each case which allows or permits any attorney (including any of the attorneys or law firms of record in the Pending Litigation) to assist, or cooperate with, any Third Party (including any current or future litigant in a litigation against Supernus) with respect to a Generic Equivalent Product. Notwithstanding the foregoing, in the ** of any ** of this Section, such ** shall not give ** any ** to ** the ** or this ** and the ** and ** for any such ** shall be an ** by such **, provided such ** shall under no circumstances **.

3.8 Supernus represents and covenants to Zydus that the Zydus License Date and the pre-marketing activities set forth in Section 3.1, ** for ** (as set for in **), and royalties rates set forth in Section 4.3 are and will be equivalent to or better than the terms granted by Supernus to any Third Party with respect to any Generic Equivalent Product ("**Third Party Agreement**"). If Supernus has entered or enters into a Third Party Agreement providing such Third Party with more favorable license effective dates, pre-marketing activities, ** for ** or royalty rates, then the applicable terms in this License Agreement shall be automatically

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amended to provide such more favorable terms to Zydus. Supernus will notify Zydus within ten (10) Business Days of entering into any such Third Party Agreement.

3.9 Should a Third Party be deemed to be a "**" (as defined in **) with respect to the **, and such ** be deemed by ** to have ** its **, then Zydus will be the ** (** as to **) ** for the ** for the first ** after such ** or is otherwise entitled to sell its **, by **, **, or **. At ** option, upon written notice delivered to ** no later than ** after the ** by the **, ** shall commence and continue to ** on a ** from the date of the ** of its ** on a ** and upon ** agreed to by ** and **. The transfer pricing for ** supplied by ** to ** will be **. The ** for ** will be ** in favor of **. For the avoidance of doubt, no ** shall be payable under ** of this License Agreement on ** of ** by **. All other terms and conditions for ** of ** will be set forth in an authorized ** agreement to be negotiated in good faith by the Parties.

3.10 Prior to the Zydus License Date, Supernus will provide written notice to Zydus within ten (10) Business Days after each time either (i) Supernus submits a document to FDA seeking a change in the Label for the Trokendi XR Product, including any specific Labeling amendments or supplements to the Supernus NDA or (ii) FDA communicates to Supernus a suggestion or directive to make a change to the Label for the Trokendi XR Product. In each case such notice shall include the text of the proposed or directed Label change.

3.11 Zydus shall use Commercially Reasonable Efforts to obtain Regulatory Approval of the Zydus ANDA.

4. Marketing of Zydus Product

4.1 **Zydus Pricing**. Zydus will have sole discretion in setting the price for the sale of the Zydus Product in the Territory.

4.2 **Scope of License Agreement**. Except to the extent permitted pursuant to Section 11.3, and without derogating from Zydus's "have Manufactured" rights set forth in Section 2.1 or the rights of Third Parties after the first sale of any Zydus Product as permitted under this Agreement, only Zydus and its Affiliates shall be permitted to Launch and Market the Zydus Product under this License Agreement.

4.3 Zydus Royalties. For any Zydus Product sold during the period commencing upon the ** and continuing until the ** of the ** of the ** as of the Effective Date in the Pending Litigation (the "Royalty Term"), Zydus will pay to Supernus a royalty as follows:

4.3.1 ** of Net Sales on Zydus Product sold (as determined by ** for other pharmaceutical products, **) during any period when the ** is ** or **;

4.3.2 ** of Net Sales on Zydus Product sold (as determined by ** for other pharmaceutical products, **) during any period when the Zydus Product is ** with ** or **;

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4.3.3 ** of Net Sales on Zydus Product sold (as determined by ** for other pharmaceutical products, **) during any period when the Zydus Product is ** with ** or **;

4.3.4 ** of Net Sales on Zydus Product sold when there are ** or ** (it being acknowledged, for the avoidance of doubt that the license granted hereunder shall be ** during any period in which this Section 4.3.4 is applicable);

4.3.5 Notwithstanding Sections 4.3.1 through 4.3.4, in the event that Zydus sells any Zydus Product after an At-Risk Launch and prior to the earlier of the Anticipated License Date or an Accelerated License Date (the "**At-Risk Period**") and ** subsequently ** a ** such ** (which ** is not subsequently ** or otherwise ** or **), the royalty on Net Sales of the Zydus Product during such At-Risk Period will be ** to ** of Net Sales on Zydus Product sold (as determined by ** for other pharmaceutical products, **, unless any such ** is subsequently **) and Zydus will pay to Supernus the ** the ** of ** actually ** by ** and ** of such Net Sales on Zydus Product; provided that the total ** by ** for sales of the Zydus Product during such At-Risk Period shall **, on a **, the ** by the ** initiating the At-Risk Launch. In the event Supernus ** a ** (other than a **) ** an **, the determination of whether the ** in the ** under this Section 4.3.5 shall be applicable will be made upon the ** of a ** concerning such **.

4.4 Royalty Payments. Payments due under this Section 4 shall be made within ** from the end of each calendar quarter in which Zydus Product is sold. All such payments shall include a report provided consistent with the antitrust laws which details the calculation of gross sales, Net Sales and the royalties payable hereunder.

4.5 Annual True-Up. Within one hundred and eighty (180) days after the end of each calendar year during the Royalty Term in which fees are payable to Supernus pursuant to this Section 4, Zydus shall perform a "true up" reconciliation (and shall provide Supernus with a written report of such reconciliation) of the items comprising deductions from Net Sales other than returns. The reconciliation shall be based on actual cash paid or credits actually issued plus an estimate for any remaining liabilities incurred related to Zydus Product but not yet paid. If the foregoing reconciliation report shows either an underpayment or an overpayment between the Parties, the Party owing payment to the other Party shall pay the amount of the difference to the other Party within thirty (30) days of the date of delivery of such report.

4.6 Final True-Up. Within twenty-five (25) months of the end of the last calendar year during the Royalty Term in which fees are payable to Supernus pursuant to this Section 4, Zydus shall perform a "true-up" reconciliation (and shall provide Supernus with a written report of such reconciliation) of the items comprising deductions from Net Sales for returns. The reconciliation shall be based on actual cash paid or credits issued for returns, through the twenty-four (24) month period following the termination of the Royalty Term. If the foregoing reconciliation report shows either an underpayment or an overpayment between the

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Parties, the Party owing payment to the other Party shall pay the amount of the difference to the other Party within thirty (30) days of the date of delivery of such report.

4.7 Maintenance of Records. Zydus shall, and shall ensure that its Affiliates shall, keep at either its normal place of business, or at an off-site storage facility, detailed, accurate and up to date records consisting of (i) records and books of account sufficient to confirm the calculation of the gross sales, Net Sales and the royalties payable hereunder; and (ii) any invoices or reports accompanying any payment to Supernus provided to Supernus in connection with this License Agreement. Such records shall be retained for a period of at least two (2) years after the end of each calendar quarter to which such records relate.

4.8 Inspection. On no less than ** notice from Supernus, Zydus shall make all the records referred to in Section 4.7 of this License Agreement available for inspection during normal business hours by an internationally recognized independent accounting firm selected by Supernus and reasonably acceptable to Zydus that is not paid in whole or in part by a contingent fee arrangement ("**Supernus' External Auditor**") for the purpose of general review or audit; provided that Supernus may not request such inspection more than once in any calendar year. Upon reasonable belief of discrepancy or dispute, Supernus' External Auditor shall be entitled to take copies or extracts from such records, and books of account (but only to the extent related to the contractual obligations set out in this License Agreement) during any review or audit, provided Supernus' External Auditor signs a confidentiality agreement with Zydus providing that such records, and books of account shall be treated as Confidential Information which may not be disclosed to Supernus or any Third Party. Supernus' External Auditor shall only disclose to Supernus the results of the Supernus' External Auditor's audit, which results shall be concurrently disclosed to Zydus. Any underpayment of amounts due hereunder as reflected by Supernus' External Auditor's results shall be promptly paid by Zydus to Supernus.

4.9 Inspection Costs. Supernus shall be solely responsible for its and Supernus' External Auditor's costs in making any such review and audit, unless Supernus' External Auditor identifies a discrepancy in the calculation of royalties paid to Supernus under this License Agreement in any calendar year from those properly payable for that calendar year of ** or greater, in which event Zydus shall be solely responsible for the cost of such review and audit and shall pay Supernus any payment due. All information disclosed by Zydus or its Affiliates pursuant to this Section 4 shall be deemed Confidential Information.

4.10 Payment Method. All payments to be made by Zydus to Supernus under this License Agreement shall be in United States dollars in immediately available funds and shall be made by wire transfer to an account designated by Supernus, such account to be designated by Supernus at least ** prior to the date any such payment is due. Any payments to be made by Supernus to Zydus under this License Agreement shall be in United States dollars in immediately available funds and shall be made by wire transfer to an account designated by Zydus for such purpose.

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4.11 Late Payments. In addition to any other rights and remedies, in the event payments required to be made under this License Agreement are not made on or prior to the required payment date, or cured within ** thereafter, the amount of the late payment shall bear interest at the lesser of ** above the prime rate reported in The Wall Street Journal (Eastern Edition) on the date such payment was due and the maximum permissible rate under the Law commencing on the date such payment is due until such date as the payment is made.

4.12 Taxes. Supernus shall be responsible for and shall pay all taxes payable on any income or any payments by Zydus to Supernus. Zydus and Supernus shall bear sole responsibility for payment of compensation to their respective personnel, employees or subcontractors and for all employment taxes and withholding with respect to such compensation pursuant to Applicable Law. Zydus shall have the right to withhold taxes in the event that the revenue authorities in any country require the withholding of taxes on amounts paid hereunder to Supernus. Zydus shall secure and promptly send to Supernus proof of such taxes, duties or other levies withheld and paid by Zydus for the benefit of Supernus. Each Party agrees to cooperate with the other Party in claiming exemptions from such deductions or withholdings under any agreement or treaty from time to time in effect.

5. Confidentiality

5.1 Confidentiality Obligation. The Parties shall keep and maintain, and shall cause their respective Affiliates and their respective employees, directors, officers, consultants and contractors to keep and maintain, as confidential any Confidential Information supplied by the other Party during the Term. The confidentiality and non-disclosure obligations contained in the Settlement Documents shall not apply to, and definition of Confidential Information shall not include, any information to the extent that such information is:

5.1.1 at the time of disclosure by one Party to the other, in the public domain or otherwise publicly known;

5.1.2 after disclosure by one Party to the other becomes part of the public domain, other than by breach by a Party of any obligation of confidentiality;

5.1.3 information which the receiving Party can establish by competent evidence was already in its possession at the time of receipt or was independently developed by the receiving Party; or

5.1.4 received from a Third Party who was lawfully entitled to disclose such information free of an obligation of confidentiality.

5.2 Exceptions. Notwithstanding Section 5.1, in addition to any disclosure allowed under Section 11.5, the Party receiving Confidential Information may disclose such Confidential Information to the extent that such disclosure has been ordered by a court of law or directed by a Governmental Authority, provided that, the disclosure is limited to the extent

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ordered or directed and wherever practicable, the Party that owns the Confidential Information has been given sufficient written notice in advance to enable it to seek protection or confidential treatment of such Confidential Information.

5.3 Expiration of Confidentiality. The confidentiality obligation contained in this Section 5 shall survive the termination or expiry of this License Agreement for so long as such Confidential Information remains confidential.

5.4 Disclosure. If a Party is subpoenaed or otherwise requested by any Person, including any Governmental Authority, (i) to give testimony or provide information which in any way relates to the Settlement Documents, or (ii) to disclose through testimony or otherwise disclose Confidential Information of the other Party which in any way relates to the Zydus Product or practices associated with the Zydus Product, then in each case such Party shall give the other Party prompt notice of such request, and unless otherwise required by Law, shall make no disclosure until such other Party has had a reasonable opportunity to contest the right of the requesting Person to such disclosure. Notwithstanding the foregoing, either Party may state publicly that the Pending Litigation has been settled on terms that are confidential.

5.5 Enforcement. The Parties agree that equitable relief, including injunctive relief and specific performance, is appropriate in enforcing the confidentiality provisions of the Settlement Documents. In the event of any such action, the prevailing Party will be entitled to recover, in addition to any charges fixed by the court, its costs and expenses of suit, including reasonable attorney's fees. Such remedies shall not be deemed to be the exclusive remedies for a breach of this provision, but shall be in addition to all other remedies available at law or equity.

6. Representations and Warranties of Parties

6.1 Supernus represents and warrants to Zydus that Supernus possess the rights and authority to grant the License and Authorization to Zydus.

6.2 Each of Supernus and Zydus represents, warrants, and covenants, to the other Party that:

6.2.1 Organization and Authority. Such Party is a corporation or other legal entity duly organized, validly existing and in good standing under the Laws of the jurisdiction of its formation. Such Party has the requisite power and authority to enter into the Settlement Documents. Such Party has the requisite power and authority to execute and deliver the Settlement Documents and to perform all of its obligations hereunder. The execution and delivery of the Settlement Documents and the performance by such Party of its obligations hereunder have been authorized by all requisite action on its part. The Settlement Documents have been validly executed and delivered by such Party, and, assuming that such documents have been duly authorized, executed and delivered by the other Party, constitutes a valid and binding obligation of such Party, enforceable against such Party in accordance with its terms.

6.2.2 Consents and Approvals. Except as otherwise set forth in this License Agreement or other Settlement Documents, no material filing with, and

no material permit, authorization, consent, or approval, of or from any Governmental Authority is required to be obtained by or on behalf of such Party with respect to the transactions contemplated by the Settlement Documents, except for those filings, permits, authorizations, consents or approvals, the failure of which to be made or obtained would not materially impair such Party's ability to consummate the transactions contemplated hereby or materially delay the consummation of the transactions contemplated hereby.

6.2.3 **No Violations**. Neither the execution nor the delivery of the Settlement Documents by such Party, nor the performance by such Party of its obligations hereunder, will (i) violate the certificate of incorporation, certificate of formation, by-laws or other organizational document of such Party; (ii) conflict in any material respect with or result in a material violation or breach of, or constitute a material default under, any material contract, agreement or instrument to which such Party is a party; or (iii) violate or conflict in any material respect with any material Law applicable to such Party.

7. **Indemnities; Product Liability; Insurance**

7.1 **Indemnity by Supernus**. Supernus shall defend, indemnify and hold harmless each of Zydus and its Affiliates and its and their directors, officers, employees and contractors (each a "**Zydus Party**") from and against any and all Losses, arising from or in connection with:

7.1.1 any Claim resulting from any negligent acts or acts of willful misconduct of any Supernus Party in connection with the performance of its obligations under this License Agreement; or

7.1.2 the breach by Supernus of any of its representations or warranties contained in this License Agreement,

except, in each case, to the extent such Losses are caused by the negligence, breach of the terms of this License Agreement, or willful misconduct of a Zydus Party.

7.2 **Indemnity by Zydus**. Zydus shall defend, indemnify and hold harmless each of Supernus and its Affiliates and its and their directors, officers, employees and contractors (each, a "**Supernus Party**") from and against any and all Losses arising from or in connection with:

7.2.1 any Claim resulting from any negligent acts or acts of willful misconduct of any Zydus Party in connection with the performance of its obligations under this License Agreement;

7.2.2 any Claim based on or arising out of the use, Manufacturing, Labeling, Packaging or Marketing of Zydus Product, including, any investigation by a Governmental Authority or any claim for personal injury or property damage

asserted by any user of Zydus Product (but ** any ** based on or arising out of any portion of the ** of the ** that, pursuant to **, is required to be the same as the ** for the **); or

7.2.3 the breach by Zydus of any of its representations or warranties contained in this License Agreement,

except, in each case, to the extent that such Losses are caused by the negligence, breach of the terms of this License Agreement, or willful misconduct of a Supernus Party.

7.3 Control of Proceedings. A Party seeking indemnification hereunder shall provide prompt written notice thereof to the other Party (and, in any event, within thirty (30) days) of the assertion of any Claim against such indemnified Party as to which indemnity is to be requested hereunder. The indemnifying Party shall have the sole control over the defense of any Claim, provided that, the indemnifying Party shall obtain the written consent of the indemnified Party prior to settling or otherwise disposing of such Claim if as a result of the settlement or Claim disposal the indemnified Party's interests are in any way adversely affected.

7.4 No Admissions. The indemnified Party shall not make any payment or incur any expenses in connection with any liability for which such Party is seeking indemnification, or make any admissions or do anything that may compromise or prejudice the defense of any Claim without the prior written consent of the indemnifying Party.

7.5 Claim Information. Each Party shall promptly:

7.5.1 inform the other by written notice of any actual or threatened Claim to which Sections 7.1 or 7.2 apply;

7.5.2 provide to the other Party copies of all papers and official documents received in respect of any such Claim; and

7.5.3 cooperate as reasonably requested by the other Party in the defense of any such Claim, provided any actual out of pocket costs incurred in connection with such cooperation shall be at the expense of the indemnifying Party.

7.6 Limitation of Liability. Except as may be included in a Claim under Section 7.1, 7.2 or 7.8, or a breach by any Party of Section 3, Section 5 or Section 11.5, in no event shall any Party or its Affiliates be liable for special, punitive, indirect, incidental or consequential loss or damage based on contract, tort or any other legal theory arising out of this License Agreement.

7.7 Product Liability Insurance. Each Party shall maintain, at its own cost, general commercial liability insurance (including comprehensive product liability) in such amount as such Party customarily maintains with respect to its other products and which is reasonable and customary in the U.S. pharmaceutical industry for companies of comparable size

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and activities, but in any event not less than $** per occurrence and $** in the aggregate. In the event the insurance policy obtained by a Party is a "claims made" policy (as opposed to an "occurrence" policy), such Party shall obtain comparable insurance for not less than ** following the expiry or termination of this License Agreement (or, in Zydus' case, the cessation of sales of the Zydus Product hereunder). Notwithstanding anything to the contrary contained herein, either Party may fulfill all of its obligations hereunder through the purchase of commercial insurance, self-insurance or through a combination of both.

7.8 Irreparable Harm. Zydus and its Affiliates acknowledge that in the event of a Zydus Launch or continued Marketing or Shipping by Zydus or its Affiliates of Zydus Product or any other Generic Equivalent Product in the Territory other than as permitted under this License Agreement, the damages to Supernus and its business (including, but not limited to, lost sales of the Trokendi XR Product) would be difficult to calculate and the adequacy of monetary damages calculated at Law would be uncertain. Accordingly, Zydus and its Affiliates agree that in any action by Supernus seeking injunctive or other equitable relief in connection with any such Zydus Launch or continued Marketing or Shipping, other than as permitted under this License Agreement, Zydus and its Affiliates shall not assert or plead the availability of an adequate remedy at Law as a defense to the obtaining of any such remedy. Zydus and its Affiliates hereby waive any equitable defense to such injunction including, laches, unclean hands, acquiescence or any estoppel arguments. The foregoing shall not be in lieu of any other remedy to which Supernus may be entitled hereunder in equity or at law as a result of such a breach.

7.9 Limitation on Representations, Warranties and Indemnification. NEITHER PARTY SHALL BE DEEMED TO MAKE ANY REPRESENTATIONS OR WARRANTIES, WHETHER EXPRESS OR IMPLIED, EXCEPT AS SPECIFICALLY SET FORTH HEREIN. ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE, ARE HEREBY DISCLAIMED BY EACH PARTY.

8. Force Majeure

8.1 Force Majeure. Neither Party shall be entitled to terminate this License Agreement or shall be liable to the other under this License Agreement for loss or damages attributable to any Force Majeure, provided the Party affected shall give prompt notice thereof to the other Party. Subject to Section 8.2, the Party giving such notice shall be excused from such of its obligations hereunder for so long as it continues to be affected by Force Majeure.

8.2 Continued Force Majeure. If any Force Majeure continues unabated for a period of at least ninety (90) days, the Parties shall meet to discuss in good faith what actions to take or what modifications should be made to this License Agreement as a consequence of such Force Majeure in order to alleviate its consequences on the affected Party.

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9. Trademarks and Trade Names

9.1 This License Agreement conveys no rights to either Party to use any trademark or trade dress of the other Party, and conveys no rights to any other intellectual property of either Party other than pursuant to the License and Authorization.

10. Term and Termination

10.1 **Term**. Unless sooner terminated in accordance with the terms hereof, the term of this License Agreement shall extend from the Effective Date until the expiration of the Licensed Patents (the "Term").

10.2 **Termination**. In addition to Supernus' right to immediately terminate this License Agreement as set forth in Section 3, either Party shall be entitled to terminate this License Agreement by written notice to the other if:

10.2.1 the other Party commits a material breach of this License Agreement, and fails to remedy it within sixty (60) days of receipt of notice from the first Party of such breach and of its intention to exercise its rights under this Section 10.2; or

10.2.2 an order is made or a resolution is passed for the winding up of the other Party (other than voluntarily for the purposes of solvent amalgamation or reconstruction) or an order is made for the appointment of an administrator to manage the other Party's affairs, business and property or if a receiver (which expression shall include an administrative receiver) is appointed over any of the other Party's assets or undertaking or if circumstances arise which entitle the court or a creditor to appoint a receiver or manager or which entitle the court to make a winding-up order or if a voluntary arrangement is proposed in respect of the other Party or if the other Party takes or suffers any similar or analogous action in consequence of debt, and such order, appointment or similar action is not removed within ninety (90) days.

10.3 **Effect of Termination**. In the event of expiry or termination of this License Agreement for any reason, each Party shall promptly return all Confidential Information of the other Party provided during the Term or destroy and certify the destruction of such Confidential Information.

10.4 **Liability on Termination**. The termination or expiry of this License Agreement shall not release either of the Parties from any liability which at the time of termination or expiry has already accrued to the other Party, nor affect in any way the survival of any other right, duty or obligation of the Parties which is expressly stated elsewhere in this License Agreement to survive such termination or expiry.

10.5 **Surviving Sections**. The provisions of Sections 1, 4.4-4.12, 5, 6, 7, 9, 10.3-10.5, 11 shall continue in force in accordance with their respective terms notwithstanding expiry or termination of this License Agreement for any reason.

11. Miscellaneous

11.1 Notice.

11.1.1 Any notice or other document given under the Settlement Documents shall be in writing in the English language and shall be given by hand or sent by prepaid overnight mail, or by confirmed fax transmission to the address of the receiving Party as set out in Section 11.2 below unless a different address or fax number has been notified to the other in writing for this purpose.

11.1.2 Each such notice or document shall: (i) if sent by hand, be deemed to have been given when delivered at the relevant address; (ii) if sent by prepaid overnight mail, be deemed to have been given one (1) Business Day after posting; or (iii) if sent by confirmed fax transmission be deemed to have been given when transmitted, provided that, a confirmatory copy of such fax or other electronic method of transmission shall have been sent by prepaid overnight mail within one (1) Business Day of such transmission.

11.2 Address for Notice. The address for services of notices and other documents on the Parties shall be:

To Supernus

Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850
Attn: President
Fax: **

with a copy to:

Edgar H. Haug
HAUG PARTNERS LLP
745 Fifth Avenue
New York, NY 10151
Fax: (212) 588-0500

To Zydus

Zydus Pharmaceutical (USA) Inc.
73 Route 31 N.
Pennington, NJ 08534
Attn: Chief Executive Officer
Fax: **

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with a copy to:

Zydus Pharmaceutical (USA) Inc.
73 Route 31 N.
Pennington, NJ 08534
Attn: Executive Vice President and Chief Legal Officer
Fax: **

and a copy to:

Michael Gaertner
LOCKE LORD LLP
111 South Wacker Drive
Chicago, IL 60606
Fax: 312-443-0336

11.3 Assignment.

11.3.1 Subject to Section 11.3.2, neither Party shall assign or transfer any of its rights or obligations under the Settlement Documents without the prior written consent of the other Party, not to be unreasonably withheld or delayed.

11.3.2 Each Party shall be entitled, without prior written consent of the other Party, to assign all, but not less than all, of its rights under the Settlement Documents to an Affiliate or transfer such rights to a successor entity by way of merger or acquisition of substantially all of the assets of such Party (whether by consolidation, sale of assets, or otherwise); provided the Affiliate or other successor entity expressly assumes in writing those rights, duties and obligations under the Settlement Documents and the Affiliate or other successor is a financially capable business entity. The assignment of the Settlement Documents by a Party and its Affiliates shall not in any way affect such Party's or its Affiliates' duties, obligations and admissions in the Settlement Documents.

11.3.3 Subject to the foregoing, the Settlement Documents shall be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns. Any assignment or transfer in contravention of the terms of the Settlement Documents shall be null and void.

11.4 Amendment. The Settlement Documents may not be varied, changed, amended, supplemented, waived, discharged or terminated, including by course of conduct or trade usage, except by an instrument in writing signed by the Party against which enforcement of such variation, change, amendment, supplement, waiver, discharge or termination is sought.

** This portion has been redacted pursuant to a confidential treatment request.

11.5 Public Announcements. The Parties shall maintain in confidence the terms of the Settlement Documents and the negotiations of the Parties pertaining thereto. Without limiting the generality of the foregoing, neither Party nor its counsel shall provide discovery (including without limitation documents, oral testimony or statements whether by deposition or otherwise, the work of outside experts or consultants, or work product embodying any of the above) to any Third Party in any judicial or arbitral proceeding pertaining to the Settlement Documents in the Territory. Notwithstanding these obligations, (i) either Party may, without the consent of the other Party, issue a press release which states publicly that the Pending Litigation has been settled, that Zydus may launch the Zydus Product on January 1, 2023 (or earlier under certain circumstances) and that the remaining terms are confidential (and such additional information as may be permitted pursuant to clause (vii) below), provided that such other Party shall be given the opportunity to review and comment on the proposed disclosure reasonably in advance of the disclosure; (ii) either Party may reference or repeat information previously disclosed in a press release or other public disclosure made in accordance with this Section 11.5; (iii) either Party may disclose such terms in discovery as otherwise required by court order, provided that the other Party shall be given the opportunity to (a) review and comment on the proposed disclosure reasonably in advance of the disclosure, and (b) quash such order and to obtain a protective order requiring that the information and documents that are the subject of such order be held in confidence by such court; (iv) either Party may disclose such terms on a need-to-know basis to such Party's actual and prospective investors, prospective acquirers, underwriters and lenders, attorneys, accountants, insurers and FDA consultants, so long as the disclosed-to entity is bound by rules of professional conduct, or has agreed in writing and in advance to maintain the confidentiality of such information under terms no less restrictive than those set forth herein; (v) Supernus may disclose the terms of the Settlement Documents to a Third Party litigant in any patent litigation or other legal proceeding (or settlements thereof) relating to the Litigated Patents or the Trokendi XR Product, (vi) Zydus may disclose such terms to the FDA as may be necessary or useful in obtaining and maintaining Regulatory Approval of the Zydus ANDA and Launching the Zydus Product as provided by the Settlement Documents, so long as Zydus requests that the FDA maintain such terms in confidence, and (vii) either Party may disclose such terms as otherwise required by Law, including without limitation securities reporting requirements, or by the rules or regulations of any stock exchange to which the Parties are subject; provided that the Parties will coordinate in advance with each other in connection with the redaction of certain provisions of the Settlement Documents with respect to any securities filings, and each Party shall use reasonable efforts to seek confidential treatment for such terms; provided, however, that each Party shall ultimately retain control over what information to disclose to the securities regulators or any other such Governmental Authorities.

11.6 Merger and Integration. The Settlement Documents supersede all prior discussions and writings of the Parties and constitute the entire agreement between the Parties with respect to the subject matter contained therein. Any breach of the License Agreement or Settlement Agreement shall constitute a breach of the Settlement Documents as a whole. Each of the Settlement Documents shall be deemed of equal dignity to each other and shall be construed together in a consistent manner as reflecting a single intent and purpose. It is agreed that: (i) neither Party has entered into any of the Settlement Documents in reliance upon any representation, warranty or undertaking of the other Party which is not expressly set out in the Settlement Documents; (ii) neither Party shall have any remedy in respect of misrepresentation

or untrue statement made by the other Party or for any breach of warranty which is not contained in Settlement Documents; and (iii) this Section 11.6 shall not exclude any liability for, or remedy in respect of, fraudulent misrepresentation.

11.7 Governing Law. The Settlement Documents shall be governed by the/ Laws of the State of New York without regard to the conflicts of law provisions thereof. The Parties irrevocably agree that the United States District Court for the Southern District of New York shall have exclusive jurisdiction to deal with any disputes arising out of or in connection with the Settlement Documents and that, accordingly, any proceedings arising out of or in connection with the Settlement Documents shall be brought in the United States District Court for the Southern District of New York. Notwithstanding the foregoing, if there is any dispute for which the United States District Court for the Southern District of New York does not have subject matter jurisdiction, the state courts in the county and state of New York shall have jurisdiction. In connection with any dispute arising out of or in connection with the Settlement Documents, each Party (i) hereby expressly consents and submits to the personal jurisdiction of the federal and state courts in the State of New York and (ii) hereby irrevocably waives any right to a trial by jury.

11.8 Agreement Costs. Each Party shall pay its own costs, charges and expenses incurred in connection with the negotiation, preparation and completion of the Settlement Documents.

11.9 Counterparts. The Settlement Documents may be executed in any number of counterparts and may be executed by the Parties on separate counterparts (including fax or electronic counterparts), each of which is an original but all of which together constitute the same instrument.

11.10 Severability. If and to the extent that any provision of the Settlement Documents is held to be illegal, void or unenforceable, such provision shall be given no effect and shall be deemed not to be included in the Settlement Documents but without invalidating any of the remaining provisions of the Settlement Documents.

11.11 Relationship of the Parties. In making and performing the Settlement Documents, the Parties are acting, and intend to be treated, as independent entities; and nothing contained in the Settlement Documents shall be construed or implied to create an agency, partnership, joint venture, or employer and employee relationship between Supernus and Zydus. Except as otherwise provided herein, neither Party may make any representation, warranty or commitment, whether express or implied, on behalf of or incur any charges or expenses for or in the name of the other Party.

11.12 Construction. The language in all parts of the Settlement Documents shall be construed, in all cases, according to its fair meaning. Supernus and Zydus acknowledge that each Party and its counsel have reviewed and revised the Settlement Documents and that any rule of construction to the effect that any ambiguities are to be resolved against the drafting Party shall not be employed in the interpretation thereof. The words “hereof,” “herein,” “hereto” and “hereunder” and words of similar import, when used in the Settlement Documents, shall refer to the agreements as a whole and not to any particular provision thereof. The terms defined in the

singular shall have a comparable meaning when used in the plural, and vice versa. Whenever used herein, the words "include," "includes" and "including" shall mean "include, without limitation," "includes, without limitation" and "including, without limitation," respectively. The masculine, feminine or neuter gender and the singular or plural number shall each be deemed to include the others whenever the context so indicates. With respect to any particular action or agreement, the use of the words "Supernus shall" or "Supernus will" herein shall also mean "Supernus shall cause" the particular action to be performed. Similarly, with respect to any particular action or agreement, the use of the words "Zydus shall" or "Zydus will" herein shall also mean "Zydus shall cause" the particular action to be performed. Nothing in the Settlement Documents shall operate to exclude any provision implied into the Settlement Documents by Law and which may not be excluded by Law or limit or exclude any liability, right or remedy to a greater extent than is permissible under Law.

11.13 Dispute Resolution.

11.13.1 Preliminary Process. If there is a disagreement between the Parties as to the interpretation of the Settlement Documents in relation to any aspect of the performance by either Party of its obligations thereunder, the Parties shall, within thirty (30) days of receipt of a written request from either Party, meet in good faith and try to resolve the disagreement without recourse to legal proceedings.

11.13.2 Escalation of Dispute. If resolution of the disagreement does not occur within ten (10) Business Days after such meeting, the matter shall be escalated to applicable Zydus and Supernus Presidents (or other ranking senior executive) for resolution.

11.13.3 Equitable Relief. Nothing in this Section 11.13 restricts either Party's freedom to seek urgent relief to preserve a legal right or remedy, or to protect a proprietary or trade secret right, or to otherwise seek legal remedies through any available channel if resolution is not otherwise achieved under this Section 11.13.

11.14 Cumulative Rights. Except as expressly set forth in the Settlement Documents, the rights and remedies of each of the Parties under or pursuant to the Settlement Documents are cumulative, may be exercised as often as such Party considers appropriate and are in addition to its rights and remedies under general law.

11.15 No Third Party Benefit. The Settlement Documents shall be binding upon and inure solely to the benefit of the Parties hereto, their Affiliates, successors and permitted assigns, and nothing in the Settlement Documents, express or implied, is intended to or shall confer upon any other Person or Persons any right, benefits or remedies of any nature whatsoever under or by reason of any of the Settlement Documents.

11.16 Further Assurance. Each of the Parties shall do, execute and perform and shall procure to be done and perform all such further acts, deeds, documents and things as the

other Party may reasonably require from time to time to give full effect to the terms of the Settlement Documents.

11.17 Waiver. No failure or delay by either Party in exercising any right or remedy provided by law under or pursuant to the Settlement Documents shall impair such right or remedy or operate or be construed as a waiver, acquiescence or variation of it or preclude its exercise at any subsequent time and no single or partial exercise of any such right or remedy shall preclude any other or further exercise of it or the exercise of any other right or remedy. A waiver by a Party of any right or remedy hereunder on any one occasion shall not be construed as a bar to any right or remedy which such Party would otherwise have on any future occasion.

[Signature Page Follows]

[Signature Page to
Settlement Agreement Regarding Extended Release Topiramate Oral Capsule Product]

IN WITNESS WHEREOF, the Parties hereto have each caused this Settlement Agreement to be executed by their authorized representatives as of the Effective Date.

SUPERNUS PHARMACEUTICALS, INC.

By: /s/ Jack Khattar

Name: Jack Khattar

Title: President & CEO

ZYDUS PHARMACEUTICAL (USA) INC.

By: _____

Name: _____

Title: _____

CADILA HEALTHCARE LIMITED

By: _____

Name: _____

Title: _____

[Signature Page to
Settlement Agreement Regarding Extended Release Topiramate Oral Capsule Product]

IN WITNESS WHEREOF, the Parties hereto have each caused this Settlement Agreement to be executed by their authorized representatives as of the Effective Date.

SUPERNUS PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____

ZYDUS PHARMACEUTICAL (USA) INC.

By: /s/ Brij Khera

Name: Brij Khera

Title: Executive Vice President &
Chief Legal Officer

CADILA HEALTHCARE LIMITED

By: /s/ Pankaj Patel

Name: Pankaj Patel

Title: Chairman & Managing Director

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SUPERNUS PHARMACEUTICALS, INC.

Plaintiff,

C.A. No. 2:14-cv-07272-SDW-SCM

v.

ZYDUS PHARMACEUTICAL (USA) INC.
and CADILA HEALTHCARE LIMITED

Defendants.

STIPULATION AND ORDER OF DISMISSAL WITHOUT PREJUDICE

This action for patent infringement having been brought by Plaintiff Supernus Pharmaceuticals, Inc. ("Supernus") against Defendants Zydus Pharmaceutical (USA) Inc., and Cadila Healthcare Limited (collectively, "Zydus").

Pursuant to Fed. R. Civ. P. 41, Supernus and Zydus by and through their undersigned counsel, hereby stipulate, that:

1. All claims, counter-claims and defenses asserted by Supernus and Zydus are dismissed without prejudice; and

2. Each party shall bear its own costs and attorneys' fees with respect to the matters dismissed hereby.

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(312) 443-0700

Attorneys for Defendants Zydus Pharmaceutical (USA) Inc. and Cadila Healthcare Limited

SO ORDERED

Dated: _____

THE HON. SUSAN D. WIGENTON
UNITED STATES DISTRICT JUDGE

EXHIBIT D

US008829186B2

(12) **United States Patent**
Dwivedi et al.

(10) **Patent No.: US 8,829,186 B2**
(45) **Date of Patent: Sep. 9, 2014**

(54) **METHOD FOR PREPARATION OF PITAVASTATIN AND PHARMACEUTICAL ACCEPTABLE SALTS THEREOF**

(71) Applicant: **Cadila Healthcare Limited**, Gujarat (IN)

(72) Inventors: **Shriprakash Dhar Dwivedi**, Gujarat (IN); **Dhimant Jasubhai Patel**, Gujarat (IN); **Alpesh Pravinchandra Shah**, Gujarat (IN); **Brij Khera**, Princeton, NJ (US)

(73) Assignee: **Cadila Healthcare Limited**, Ahmedabad (IN)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/665,932**

(22) Filed: **Nov. 1, 2012**

(65) **Prior Publication Data**

US 2013/0059885 A1 Mar. 7, 2013

Related U.S. Application Data

(62) Division of application No. 13/009,492, filed on Jan. 19, 2011, now abandoned.

(30) **Foreign Application Priority Data**

Jan. 20, 2010 (IN) 159/MUM/2010

(51) **Int. Cl.**
C07D 215/14 (2006.01)

(52) **U.S. Cl.**
CPC ***C07D 215/14*** (2013.01)
USPC **546/10**; 546/173

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

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2009/0275752	A1*	11/2009	Reddy et al.	544/297
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FOREIGN PATENT DOCUMENTS

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WO	2007132482	A2	11/2007

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Acemoglu et al., A New and Efficient Synthesis of the HMG-CoA Reductase Inhibitor Pitavastatin, 90(6) Helvetica Chimica Acta 1069-1081 (2007).*

Takahashi et al., "Synthesis of an Artificial HMG-CoA Reductase Inhibitor NK-104 via a Hyrosilylation-Cross-Coupling Reaction" Bull. Chem. Soc. Jpn. 68(9):2649-2656 (1995).

Suzuki M et al; "Synthesis and Biological Evaluations of Quinoline-based HMG-CoA Reductase Inhibitors", Bioorganic & Medicinal Chemistry, Pergamon, GB, vol. 9, No. 10, Jan. 1, 2001, pp. 272727-272743.

Takahashi K et al: "A New Synthesis of HMG-CoA Reductase Inhibitor NK-104 Through Hydrosilylation-Cross Coupling Reacation", Tetrahedron Letters, Elsevier, Amsterdam, NL, vol. 34, No. 51, Jan. 1, 1993, pp. 8263-8266.

Hiyama T et al: "Synthesis of Artificial HMG-CoA Reductase Inhibitors Based on the Olefination Strategy", Bulletin of the Chemical Society of Japan, Chemical Society of Japan, Tokyo, Japan, vol. 68, No. 1, Jan. 1, 1995, pp. 364-372.

European Patent Office acting as the International Search Authority under the Patent Cooperation Treaty, International Search Report, PCT/IN2011/000039, Oct. 28, 2011.

* cited by examiner

Primary Examiner — Janet L Andres
Assistant Examiner — Timothy R Rozof
(74) *Attorney, Agent, or Firm* — Brij Khera; William D. Hare, Esq.; McNeely, Hare & War, LLP

(57) **ABSTRACT**

The present invention discloses a compound, which is alkali or alkaline earth metal salts of pitavastatin, wherein the alkali or earth metal comprise one or more of magnesium, zinc, potassium, strontium and barium.

30 Claims, 4 Drawing Sheets

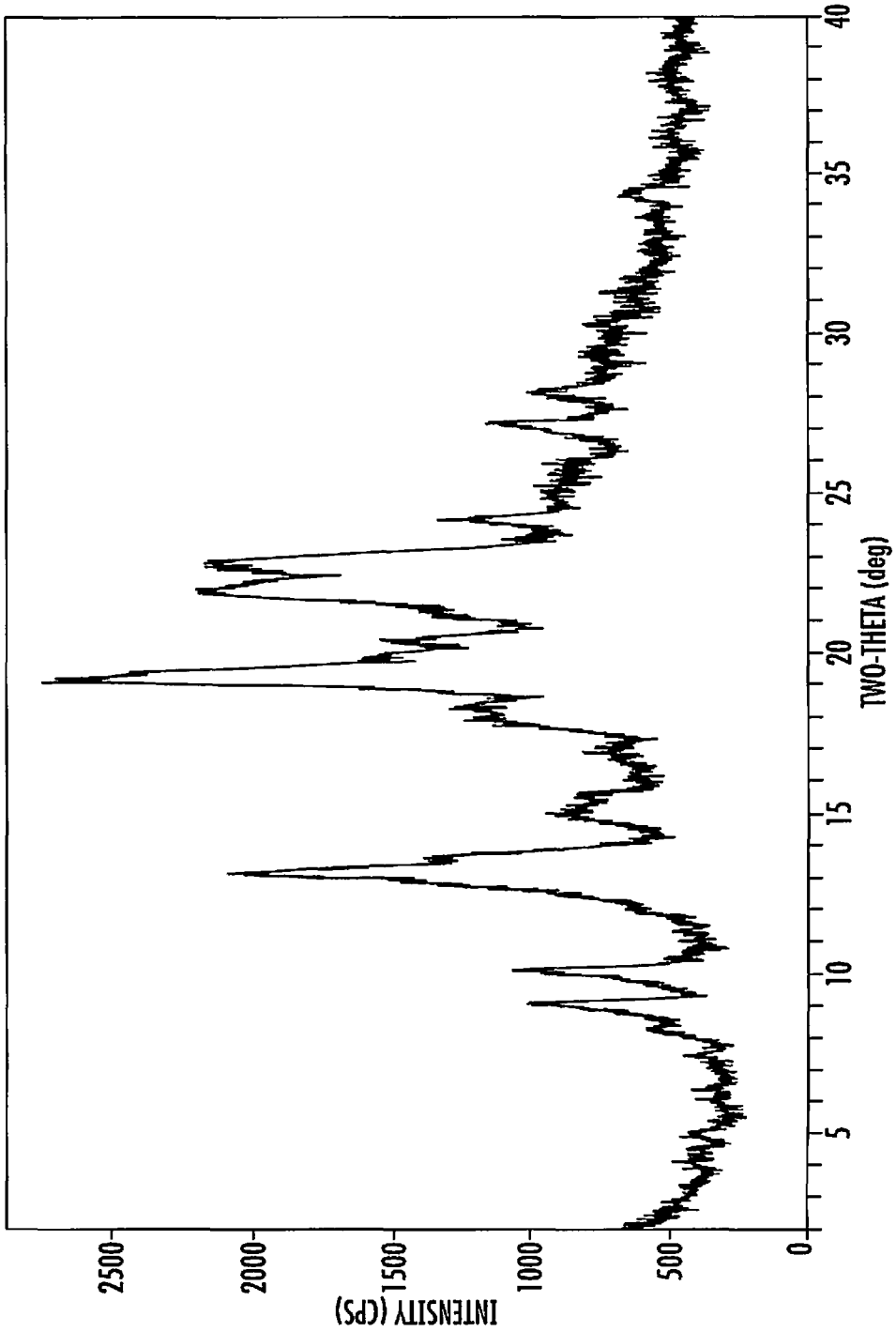
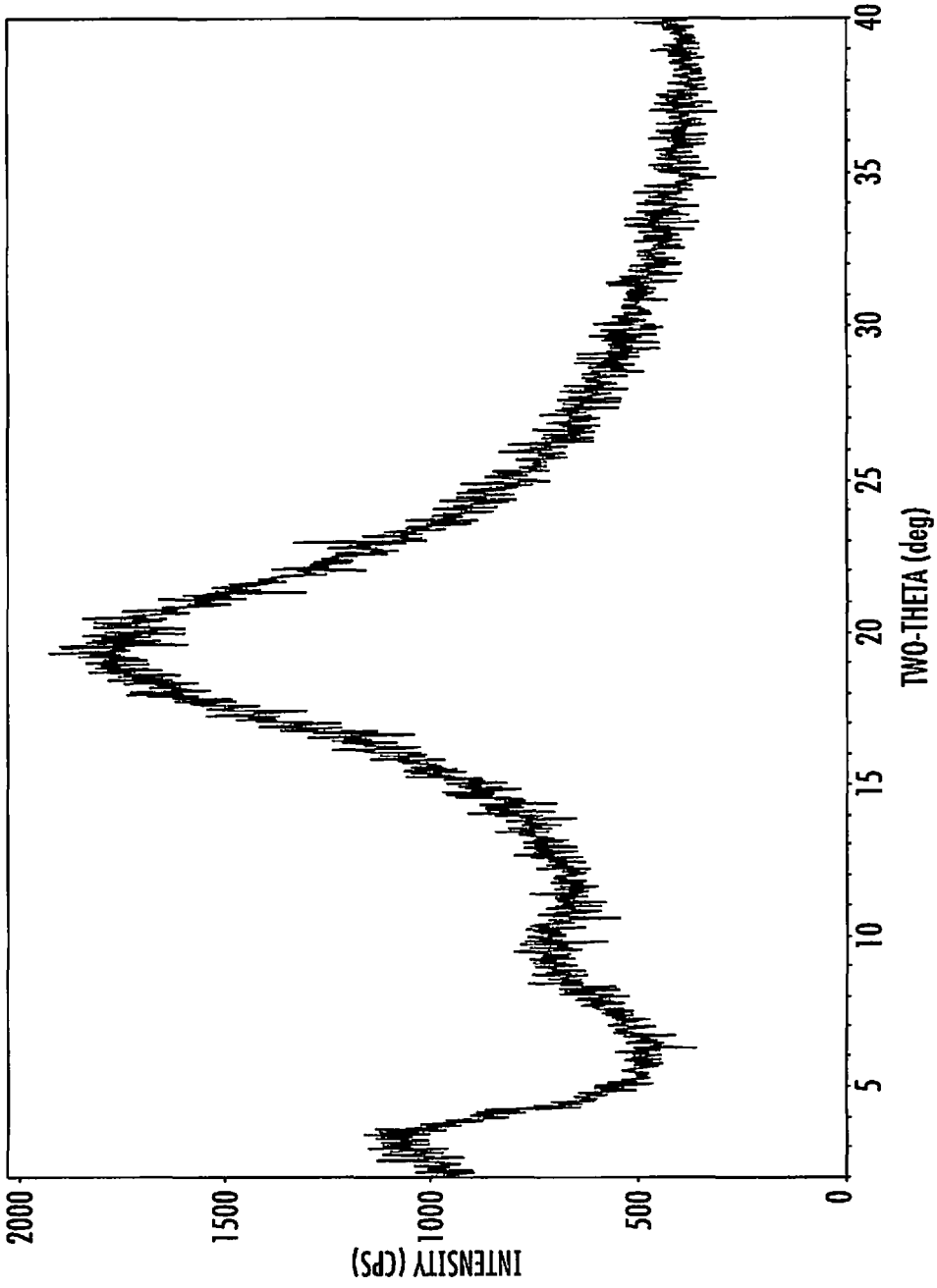

INTENSITY (CPS)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
TWO-THETA (deg)

FIG. 1


INTENSITY (CPS)
2000
1500
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10
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35
40
TWO-THETA (deg)

FIG. 2

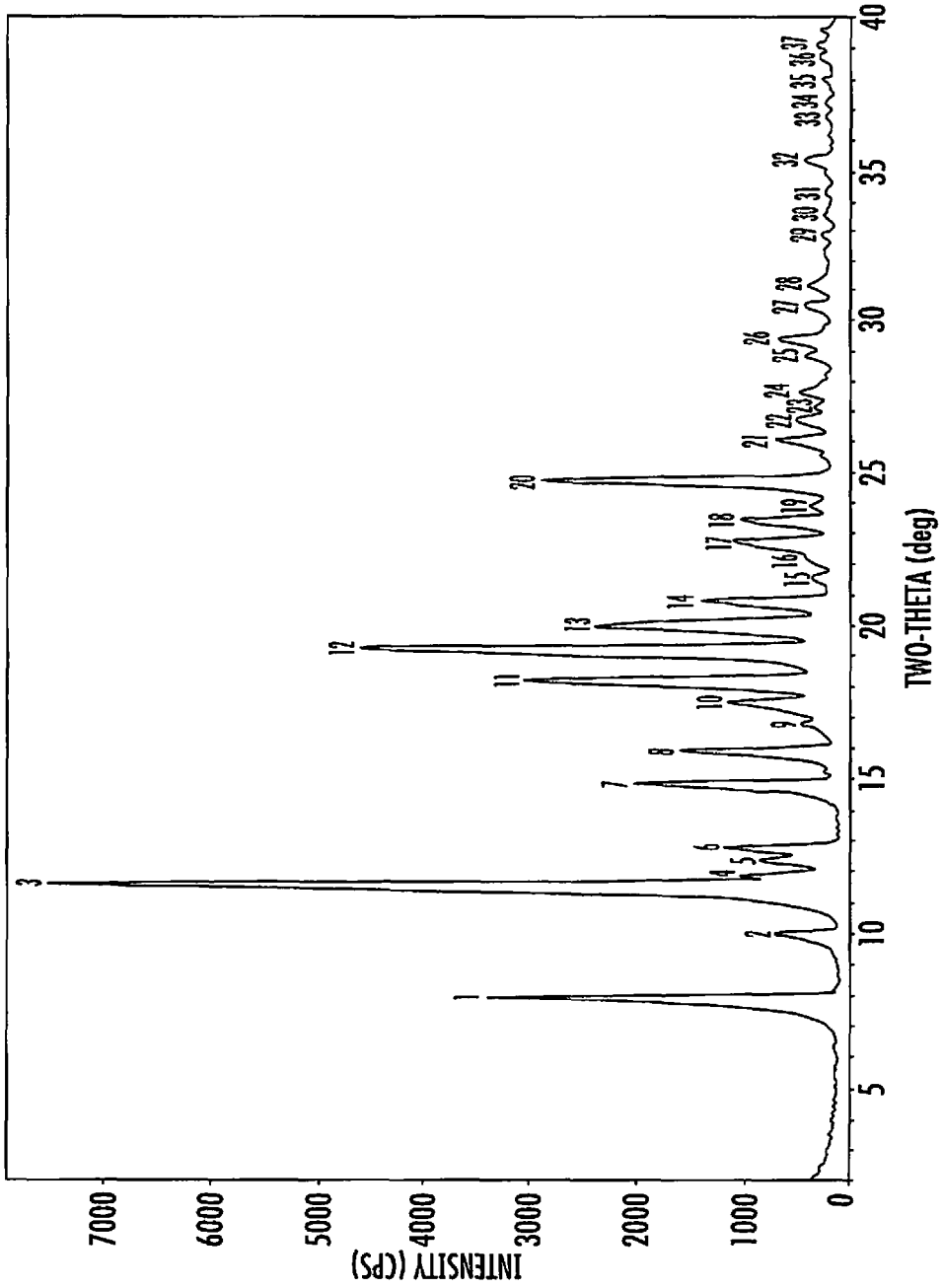

INTENSITY (CPS)
0
1000
2000
3000
4000
5000
6000
7000
TWO-THETA (deg)
5
10
15
20
25
30
35
40

FIG. 3

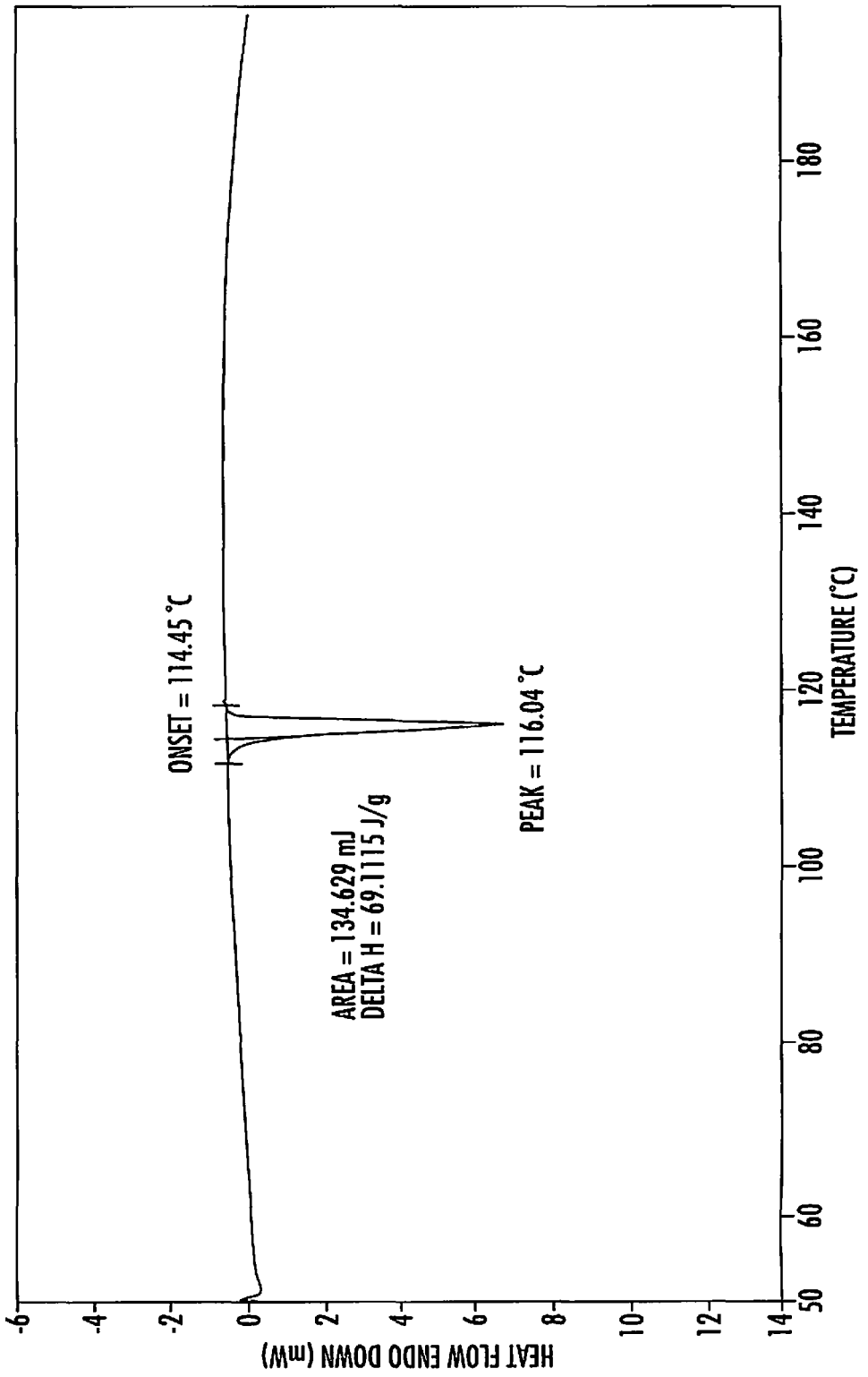

ONSET = 114.45 °C
PEAK = 116.04 °C
AREA = 134.629 mJ
DELTA H = 69.1115 J/g
HEAT FLOW ENDO DOWN (mW)
TEMPERATURE (°C)
-6
-4
-2
0
2
4
6
8
10
12
14
50
60
80
100
120
140
160
180

FIG. 4

METHOD FOR PREPARATION OF PITAVASTATIN AND PHARMACEUTICAL ACCEPTABLE SALTS THEREOF

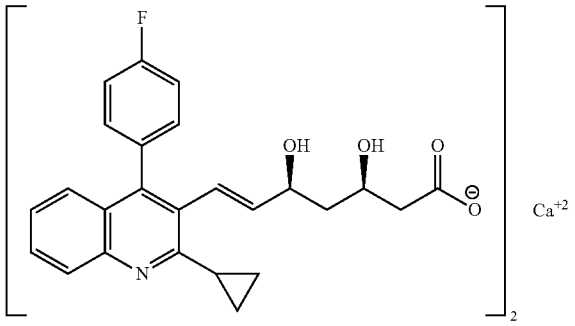
FIELD OF THE INVENTION

The present invention relates to processes for the preparation of pitavastatin and pharmaceutically acceptable salts thereof. In particular, the present invention provides processes for the preparation of pitavastatinalkali or alkaline earth metal salts in crystalline and amorphous forms.

BACKGROUND OF THE INVENTION

Pitavastatin calcium is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt having the formula IA is known in the literature.

(IA)



Pitavastatin is a synthetic lipid-lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase (HMG-CoA Reductase inhibitor). This enzyme catalyzes the conversions of HMG-CoA to mevalonate, inhibitors are commonly referred to as "statins". Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. Pitavastatin is used in the treatment of hyperchloesterolemia and mixed dyslipidemia.

Pitavastatin calcium has recently been developed as a new chemically synthesized and powerful statin by Kowa Company Ltd, Japan. On the basis of reported data, the potency of Pitavastatin is dose-dependent and appears to be equivalent to that of Atorvastatin. This new statin is safe and well tolerated in the treatment of patients with hypercholesterolaemia. Significant interactions with a number of other commonly used drugs can be considered to be extremely low.

Processes for the preparation of Pitavastatin are described in EP-A-0304063 and EP-A-1099694 and in the publications by N. Miyachi et al. in Tetrahedron Letters (1993) vol. 34, pages 8267-8270 and by K. Takahashi et al. in Bull. Chem. Soc. Japan (1995) Vol. 68, 2649-2656. These publications describe the synthesis of Pitavastatin in great detail but do not describe the hemi-calcium salt of Pitavastatin. The publications by LA. Sorbera et al. in Drugs of the Future (1998) vol. 23, pages 847-859 and by M. Suzuki at al. in Bioorganic & Medicinal Chemistry Letters (1999) vol. 9, pages 2977-2982 describe Pitavastatin calcium, however, a precise procedure for its preparation is not given. A full synthetic procedure for the preparation of Pitavastatin calcium is described in EP-A-0520406. In the process described in this patent Pitavastatin calcium is obtained by precipitation from an aqueous solution as a white crystalline material with a melting point of 190-192° C.

US20090182008 A1 discloses polymorphic form A, B, C, D, E, and F, and the amorphous form of Pitavastatin Calcium salt (2:1). In particular, crystalline Form A having water content from about 5% to about 15% and process for its preparation are disclosed.

US20090176987 A1 also discloses polymorphic form crystal form A of Pitavastatin Calcium which contains from 5 to 15% of water and which shows, in its X-ray powder diffraction as measured by using CuKα radiation, a peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

WO2007/132482 A1 discloses a novel process for the preparation of Pitavastatin Calcium by condensing bromide salt of formula-3 with aldehyde compound of formula-4 to obtain olefinic compound of formula-5 and converting olefinic compound to Pitavastatin Calcium via organic amine salt for purification.

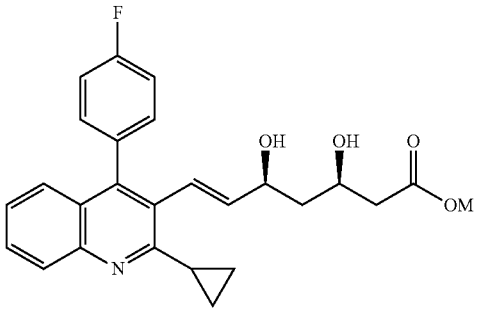
There are no reports available in the prior art for the preparation of Pitavastatin Magnesium. Thus, the inventors of the present inventions provide a novel pharmaceutically acceptable salt of Pitavastatin, preferably magnesium salt.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided alkali or alkaline earth salt of quinoline derivatives such as pitavastatin, a HMG-CoA inhibitors, more specially, the present invention provides a novel process for the preparation of pitavastatinmagnesium it is crystalline and amorphous form.

In one embodiment, there is provided a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salts. In particular, pitavastatinalkali or alkaline earth metal comprises one or more of magnesium, zinc, potassium, strontium, barium and the like. Pitavastatin, which is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid and its pharmaceutically acceptable salts having the general formula I

(I)

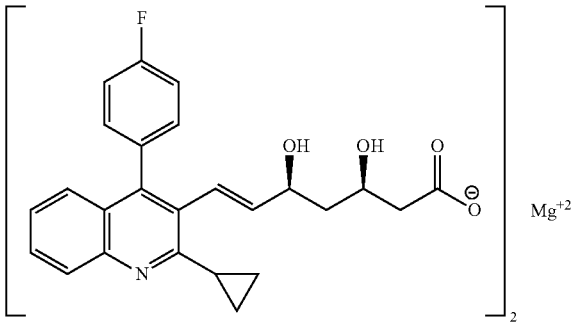


wherein, M is K^+, Mg^{+2}, Sr^{+2}, Zn^{+2}, Ba^{+2}.

In one preferred embodiment, there is provided a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salts, particularly pitavastatinmagnesium which is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid Magnesium salt having the formula IB.

In second embodiment, there is provided a novel salt, pitavastatinmagnesium of Formula (IB)

(IB)



In yet another embodiment, there is provided pitavastatinmagnesium it its crystalline form having X-ray powder diffraction peaks at 10.1, 13.2, 19.3 and 27.2±0.2 (2θ).

In further embodiment, there is provided a process for the preparation of pitavastatinmagnesium of formula (1B), the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-II;

(b) hydrolyzing the compound of Formula-II under the acidic conditions to remove the acetonide protection to form a diol compound;

(c) treating the diol compound of step (b) in-situ with an alkali metal hydroxide to form the corresponding alkali metal salt of pitavastatin (I);

(d) treating alkali metal salt of pitavastatin with a magnesium source to obtain pitavastatinmagnesium; and

(e) isolating the pitavastatinmagnesium.

According to the embodiments, the process for the preparation of pitavastatinmagnesium according to the present inventions provides crystalline form of pitavastatinmagnesium having water content in the range of from about 7% to about 12% wt/wt.

According to another embodiment, the compound (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester of formula (II) in crystalline form.

According to another embodiment, there is provided an improved process for the purification of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester of formula (II) to obtain in crystalline form.

According to the further embodiments, there is provided a process for the preparation of pitavastatinmagnesium in amorphous form, the process comprising:

(a) providing a solution comprising pitavastatinmagnesium in a suitable organic solvent wherein the organic solvent is one or more of a chlorinated solvent, alcoholic solvent, ketonic solvent, aliphatic or cyclic ether and mixtures thereof;

(b) adding suitable antisolvent to the solution; and

(c) recovering the amorphous form of the pitavastatinmagnesium.

According to the further embodiments, there is provided a process for the preparation of an amorphous form of the pitavastatinmagnesium having water content less than about 2% wt/wt,

the process comprising:

(a) providing pitavastatinmagnesium in crystalline form having water content in the range of about 8% to about 12% wt/wt;

(b) contacting the pitavastatinmagnesium with humid air in a fluidized bed drier, or maintaining the pitavastatinmagnesium at a temperature of from about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 to 5 days; and

(c) recovering the pitavastatinmagnesium in the amorphous form having water content less than about 2% wt/wt.

According to the further embodiment, there is provided substantially pure pitavastatinmagnesium in stable crystalline form.

DETAILED DESCRIPTION OF DRAWINGS

FIG. **1**: X-ray diffraction pattern of crystalline pitavastatinmagnesium having about 8% to about 12% water content prepared as per the process of Example-2

FIG. **2**: X-ray diffraction pattern of amorphous pitavastatinmagnesium prepared as per the process of Example-3

FIG. **3**: X-ray diffraction pattern of crystalline (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound (II).

FIG. **4**. DSC thermogram of crystalline (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound (II) having endothermic peak at about 116.04° C.

The details of one or more embodiments of the inventions are set forth in the description below.

Other features, objects and advantages of the inventions will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The prior art discloses the use of organic amine salts of Pitavastatin for obtaining better purity. The present inventors have found that pitavastatinalkali or alkaline earth metal salt prepared by using the process provided herein provides better yield and purity and avoids the use of amine salt formation. This significantly improves the process economics and commercial viability.

As used here in the term "isolation" may include filtration, filtration under vacuum, centrifugation, and decantation. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

Optionally, the solution, prior to any solids formation, can be filtered to remove any undissolved solids, solid impurities and the like prior to removal of the solvent. Any filtration system and filtration techniques known in the art can be used.

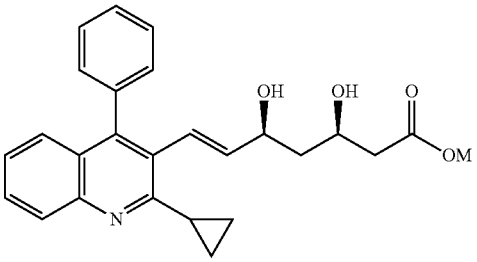
The term "Suitable organic solvent" means a single or a combination of two or more solvents.

The term "Substantially pure" means pitavastatinalkali or alkaline earth metal prepared by the process of the present invention is substantially free from any single individual impurities like desfluoro impurity, cis-isomer impurity, Pitavastatin 5-oxo impurity, pitavastatinlactone impurity, pitavastatin t-butyl diol ester impurity, and pitavastatincondensed impurity.

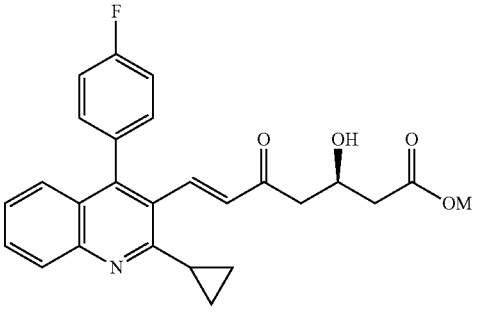
Further the term "substantially pure" means pitavastatinalkali or alkaline earth having purity greater than 99%. In particular, it may be greater than 99.5% by area percentage of HPLC. In particular, containing less than about 0.1% of single individual impurity as herein described above and total impurities not more than 1.0% by area percentage of HPLC.

Particularly, pitavastatindiastereomeric impurity and pitavastatinenantiomeric impurity are present less than about 0.3% by area percentage of HPLC.

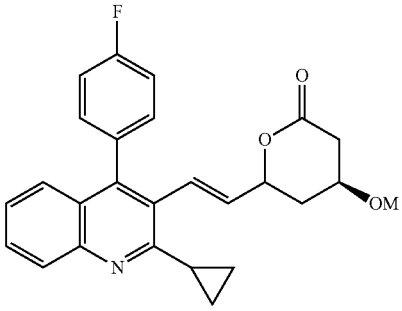
The above impurities are present in the preparation of pitavastatinalkali or alkaline earth metal salts includes the following which were determined from an HPLC analysis of different batches of pitavastatinalkali or alkaline earth metal salts produced by the method described in the specification herein after:



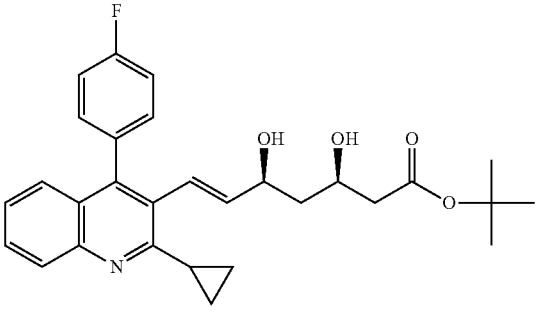
Des-Flouro Pitavastatin



Pitavastatin 5-oxo Impurity

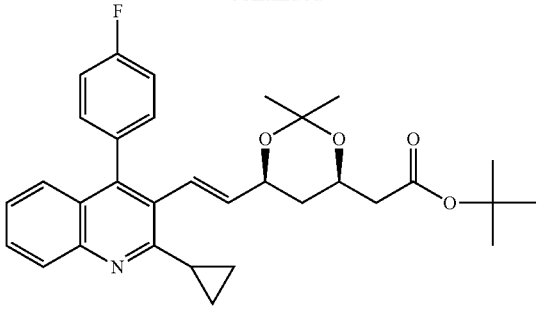


Pitavastatin Lactone Impurity

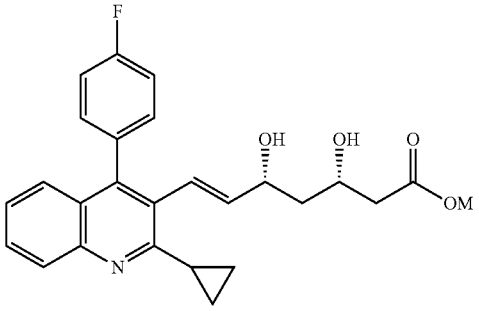


Pitavastatin t-butyl diol ester Impurity

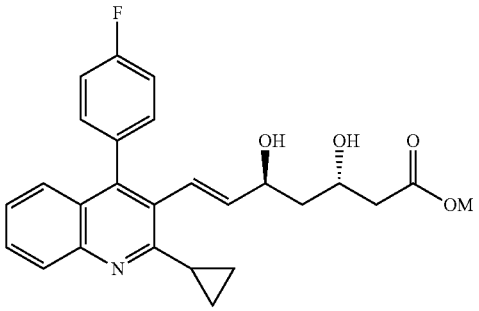
-continued



Pitavastatin Condensed Impurity



Pitavastatin Diastereomer Impurity

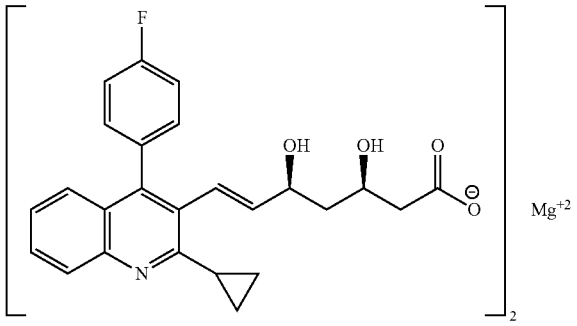


Pitavastatin Enantiomeric Impurity

In first embodiment, there is provided alkali or alkaline earth metal salts of pitavastatin, wherein the alkali or alkaline earth metal comprises one or more of magnesium, zinc, potassium, strontium, barium and the like. In particular, it may comprises one or more of magnesium, zinc and potassium.

In second embodiment of the present invention, there is provided a novel salt pitavastatin magnesium of Formula (IB)

(IB)



In particular, the pitavastatin magnesium may be a hydrate having water content in the range of from about 7% to about 12% wt/wt. In particular, the water content may be about 9% to about 12% wt/wt. More particularly, the water content may be about 10% to about 12% wt/wt as measured by the known techniques in the art like Karl-Fisher method.

In yet another embodiment, there is provided pitavastatin magnesium in crystalline form having x-ray powder diffraction peaks at 10.1, 13.2, 19.3 and 27.2±0.2 (2θ). In particular, the pitavastatin magnesium crystalline form is having an x-ray powder diffraction pattern as shown in FIG. **1**. Further embodiment includes pitavastatin magnesium having optical rotation of about +22.0 to +22.5 in 1% DMSO at 20±0.5° C.

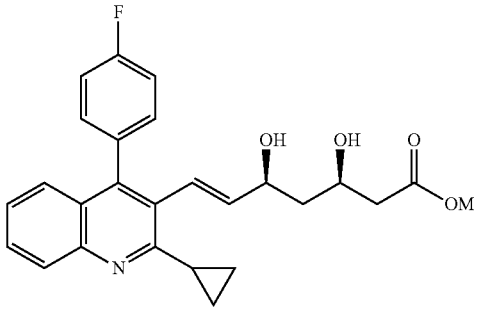
In yet another embodiment, there is provided an amorphous form of the pitavastatin magnesium having x-ray powder diffraction peaks as shown in FIG. **2**.

According to further embodiment, the amorphous form of pitavastatin magnesium is having the water content less than about 5% wt/wt. In particular, it may have the water content less than about 2% wt/wt.

In a third embodiment, there is provided a process for the preparation of pitavastatin and its pharmaceutically acceptable salts, in particularpitavastatin alkali or alkaline earth metal comprises one or more of magnesium, potassium, zinc and the like.

The pitavastatinalkali metal salts is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid salt having the general Formula (I)

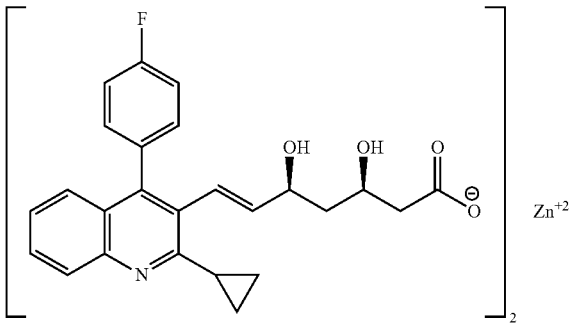
(I)



wherein, M is Na^+, K^+, Li^+.

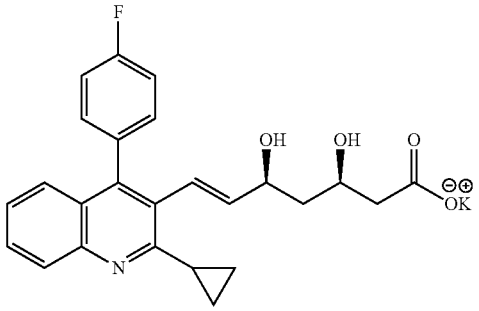
In a further embodiment of the present invention, there is provided a pitavastatinzinc of Formula (IC)

(IC)



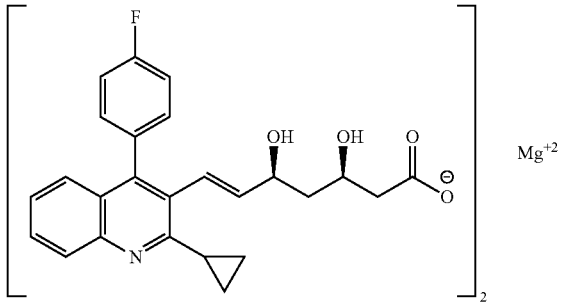
In yet another aspect of the present invention, there is provided a pitavastatinpotassium of formula (ID)

(ID)



According to a further embodiment, there is provided a process for the preparation of pitavastatinmagnesium of formula (1B),

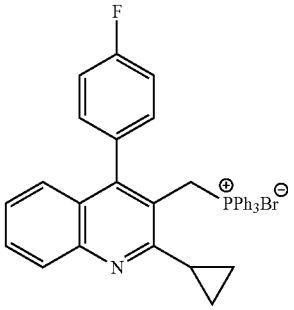
(IB)



the process comprising:

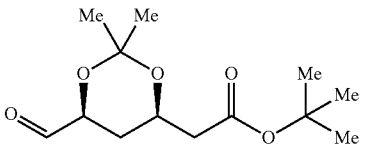
(a) reacting phosphonium bromide compound of Formula-IV

(IV)



with an aldehyde compound of Formula-III

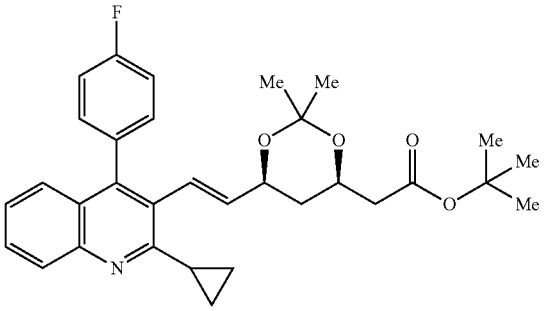
(III)



in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vi-

nyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-II,

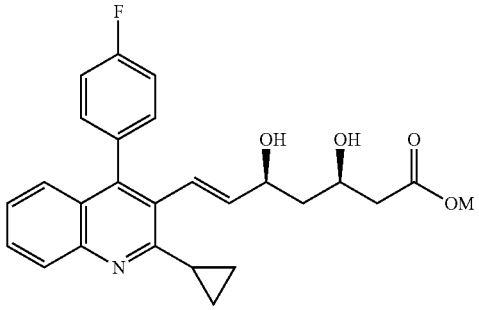
(II)



(b) hydrolyzing the compound of Formula-II under the acidic conditions to remove acetonide protection to form diol compound;

(c) treating the diol compound of step (b) in-situ with an alkali metal hydroxide to form the corresponding alkali metal salt of Pitavastatin (I);

(I)



wherein, M is Na^+, K^+, Li^+;

(d) treating the alkali metal salt of pitavastatin (I) with a magnesium source to obtain pitavastatinmagnesium; and

(e) isolating the pitavastatin magnesium.

The phosphonium bromide compound of Formula-IV and aldehyde compound of Formula-III can be reacted in the presence of alkali or alkaline earth metal bases. The alkali or alkaline earth metal bases comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate and the like. In particular, it may be potassium carbonate.

Embodiments includes that the reaction may be performed in a suitable polar aprotic solvent comprises one or more dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methylpyrrolidone or mixtures thereof. In particular, it may be dimethylsulfoxide. The reaction may be performed at an ambient temperature i.e. at about 15° C. to about 40° C. In particular, it may be from about 20° C. to about 35° C.

The reaction mixture may be stirred for about 5 to 15 hours till completion of the reaction, in particular for 10 hours. The reaction mixture may be further treated with suitable organic solvents like toluene, xylene, methylene dichloride, ethyl acetate for extracting the compound of Formula-II. Particularly, the compound of Formula-II is extracted by using toluene.

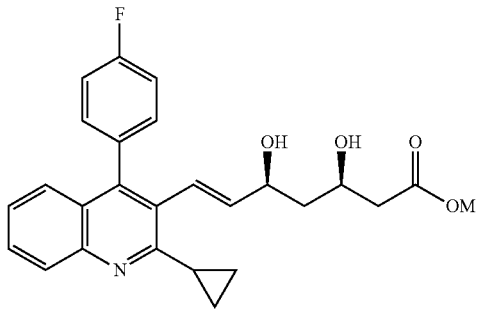
In general, the compound of Formula-II may be isolated by removal of toluene followed by addition of isopropanol. After the addition of isopropanol, the reaction mixture can be heated to 40° C. to 80° C., preferably 60° C. to 70° C. and cooling to 15° C. to obtain olefin compound of Formula (II). The compound of Formula (II) may optionally be purified in suitable polar solvent like methanol, ethanol, Isopropanol, acetone, DMF, ethyl acetate, butyl acetate and the like. In particular, the compound of Formula (II) may be purified using methanol.

Further embodiments of the process include, hydrolysis of compound of Formula (II). The hydrolysis of olefin compound is done under the acidic conditions to remove the acetonide protection and to form diol compound. The suitable acids comprise one or more of hydrochloric acid, acetic acid, sulfuric acid, nitric acid, phosphoric acid and the like. In particular it may be hydrochloric acid.

The diol compound obtained is in-situ treated with an alkali metal hydroxide selected from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like.

In particular it may be sodium hydroxide to obtain corresponding alkali metal salt of pitavastatin (I)

(I)



herein M is Na^+.

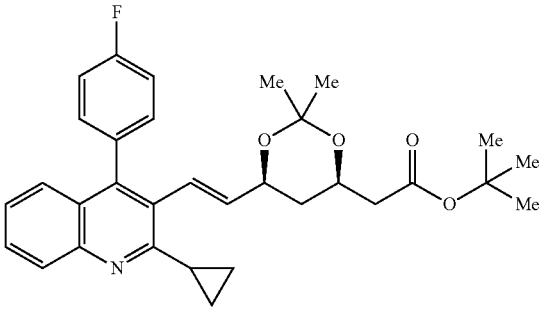
Embodiments of the process includes treating alkali metal salt of formula (I) of pitavastatin, in particular it may be pitavastatinsodium with magnesium source. Preferred magnesium source comprises one or more of magnesium chloride, magnesium methoxide, magnesium acetate and hydrates thereof. In particular, it may be magnesium chloride hexahydrate.

In general, the pitavastatinmagnesium prepared by the method as described above, can be dried in hot air oven at 40° C. to 45° C. for at least about 4 to 24 hours having water content in the range of about 8% to 12% wt/wt to obtain pitavastatinmagnesium in crystalline form.

Embodiments further includes, drying pitavastatin magnesium having water content in the range of about 8% to about 12% wt/wt for about 8 hours or more; in particular, for at least about 24 hours so as obtain substantially anhydrous pitavastatin magnesium having water content less than about 2% wt/wt.

According to the preferred embodiment, there is provided an improved process for the preparation of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester of Formula (II),

(II)



the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of Formula-II,

(b) treating compound of Formula-II with one or more suitable polar solvent to form reaction mixture;

(c) heating the reaction mixture at an elevated temperature;

(d) cooling the reaction mixture to ambient temperature; and

(e) isolating the (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester in crystalline form.

The phosphonium bromide compound of Formula-IV and aldehyde compound of Formula-III can be reacted in the presence of alkali or alkaline earth metal base. The alkali or alkaline earth metal base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate and the like. In particular, it may be potassium carbonate.

Embodiments includes that the reaction can be performed in one or more of suitable polar aprotic solvent selected from dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methylpyrrolidone or mixtures thereof. In particular it may be dimethylsulfoxide at an ambient temperature i.e. at about 15° C. to about 40° C. In particularly, it may be from about 20° C. to about 35° C.

The reaction mixture can be stirred for about 5 to 15 hours till completion of the reaction. In particular, it may be for 10 hours. The reaction mixture can be further treated with suitable organic solvents like toluene, xylene, methylene dichloride, ethyl acetate for extracting compound of Formula-II. In particular, the compound of Formula (II) may be extracted with toluene.

The compound of Formula-II can be isolated by removal of toluene followed by addition of isopropanol. After the addition of isopropanol, the reaction mixture can be heated to 40° C. to 80° C., particularly at about 60° C. to 70° C. and cooling to 15° C. to obtain compound of formula (II). The compound of formula (II) can be purified in suitable polar solvent like methanol, ethanol, Isopropanol, acetone, DMF, ethyl acetate, butyl acetate and the like. In particular, it may be methanol.

In general, the term "elevated temperature" includes heating the compound II in a polar solvent at about 50° C. to about 100° C. In particular, the compound II may be heated at about 50° C. to about 70° C., most particularly, at about 60° C. to 65° C.

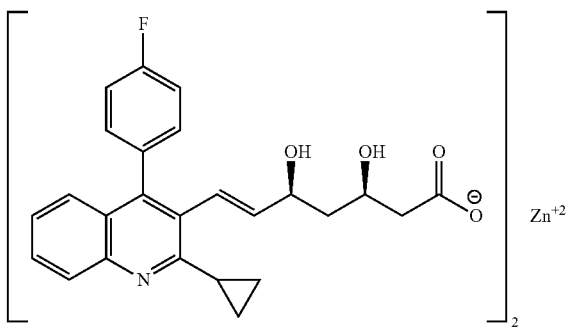
In general, the term "ambient temperature" includes cooling the reaction mixture comprising the compound II in a polar solvent at about 0° C. to about 30° C. In particular, it may be at about 0° C. to about 15° C., most particularly, at about 0° C. to 10° C. According to the embodiment, the compound (II) i.e. (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester is obtain in crystalline form after purification in polar solvent.

The crystalline form of compound (II) is characterized by an X-ray powder diffraction pattern having characteristics peaks expressed in degrees 2θ (±0.2° 2θ) at 7.86°, 9.94°, 11.48°, 12.71°, 14.80°, 15.88°, 17.44°, 18.16°, 19.17°, 19.97°, 20.77°, 22.71°, 23.41°, 24.68°, 26.02°, 27.63° and 29.36°±0.2°. The X-ray powder diffraction pattern is characterized substantially the same that shown in FIG. **3**.

The crystalline form of compound (II) is characterized by an IR spectrum having peaks at about 2999, 2976, 1720, 1600, 1512, 1487, 1379, 1342, 1288, 1197, 1134, 1066, 1035, 931 and 842 cm^{-1} and DSC endotherm at about 116.04° C. The DSC thermogram is substantially the same that shown in FIG. **4**.

According to the further embodiment, there is provided a process for the preparation of pitavastatinzinc of formula (IC),

(IC)



the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-II;

(b) hydrolyzing the compound of Formula-II under the acidic conditions to remove the acetonide protection to form diol compound;

(c) treating the diol compound of step (b) in-situ with an alkali metal hydroxide to form the corresponding alkali metal salt of pitavastatin (I);

(d) treating the alkali metal salt of pitavastatin (I) with a zinc source to obtain Pitavastatinzinc; and

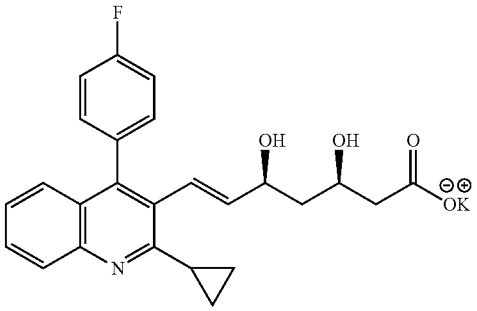
(e) isolating the pitavastatinzinc.

In general, the process parameters for the preparation of compound (II) and its hydrolysis are similar as discloses herein above. The preferable zinc source comprises one or more of zinc formate, zinc acetate, zinc propionate, zinc maleate, zinc fumarate, zinc tartrate, zinc lactate, zinc malate, zinc citrate, Zinc ascorbate, zinc malonate, zinc oxalate, zinc glycolate, zinc methanesulfonate, zinc ethanesulfonate, a salt

of zinc with amino acid, zinc sulfate, zinc chloride, zinc carbonate or zinc nitrate. In particular, it comprises one or more of zinc sulfate, zinc chloride or zinc acetate.

According to the further aspect, there is provided a method for the preparation of pitavastatinpotassium of formula (ID),

(ID)



the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal bases in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of Formula-II,

(b) hydrolyzing the compound of Formula-II by subjecting under the acidic conditions to remove the acetonide protection to form diol compound;

(c) treating the diol compound of step (b) in-situ with a potassium source to obtain pitavastatinpotassium.

In general, the process parameters for the preparation of compound (II) and its hydrolysis are similar as discloses herein above. The preferable potassium source comprises one or more of potassium hydroxide, potassium carbonate, potassium bicarbonate, potassium acetate, potassium chloride and the like.

According to the further embodiment, there is provided a process for the preparation of amorphous form of pitavastatinmagnesium, the process comprising:

(a) providing a solution comprising pitavastatinmagnesium in a suitable organic solvent wherein the organic solvent is selected from the group consisting of a chlorinated solvent, alcoholic solvent, ketonic solvent, esters solvent and mixtures thereof;

(b) removing the organic solvent to obtain residue;

(c) adding a suitable anti-solvent to the residue; and

(d) recovering the amorphous form of the pitavastatinmagnesium.

The amorphous form can be generally prepared by addition of anti-solvent to a concentrated solution of pitavastatinmagnesium in an organic solvent.

Embodiments of the process includes preparing the solution of pitavastatinmagnesium in suitable organic solvent selected from the group consisting of a chlorinated solvent, alcoholic solvent, ketonic solvent, ester solvents and mixtures thereof. The preferred solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, and mixtures thereof or mixture thereof with water. In particular, the suitable solvent comprises one or more of methanol, acetone, ethyl acetate.

In general, the embodiment of the process includes adding suitable antisolvent to the solution of pitavastatinmagnesium in suitable organic solvent. The suitable anti-solvent comprises one or more of hexane, heptane, cyclohexane, toluene, xylene, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and the like. In particular, the suitable anti-solvent comprises one or more of heptane or cyclohexane or methyl tert-butyl ether.

According to the embodiment, there is provided a process for the preparation of amorphous form of pitavastatinmagnesium, the process comprising:

(a) providing a solution comprising pitavastatinmagnesium in a suitable organic solvent wherein the organic solvent is one or more of a chlorinated solvent, alcoholic solvent, ketonic solvent, esters solvent and mixtures thereof;

(b) heating reaction mixture at an elevated temperature followed by cooling to ambient temperature;

(c) adding a suitable anti-solvent to the solution; and

(d) recovering the amorphous form of pitavastatinmagnesium.

In general, the suitable solvents and anti-solvents comprises from the same as listed herein above. However, the reaction mixture can be heated to an elevated temperature in step (b). The elevated temperature is from about 50° C. to about 100° C. In particularly, it may be from about 70° C. to about 90° C.

The reaction mixture is then cooled to an ambient temperature, preferably from about 15° C. to about 35° C., preferably from about 25° C. to 35° C.

It is preferable that the anti-solvent and solvent are miscible. The amorphous form can also be prepared by lyophilization of or removal of solvent from the solution of pitavastatinmagnesium in a suitable solvent.

According to the further embodiments, there is provided a process for the preparation of amorphous form of pitavastatinmagnesium having water content less than about 2% wt/wt, the process comprising:

(a) providing pitavastatinmagnesium in crystalline form having water content in the range of about 8% to about 12% wt/wt;

(b) contacting the pitavastatinmagnesium with humid air in a fluidized bed drier, or maintaining the pitavastatinmagnesium at a temperature of from about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 to 5 days; and

(c) recovering the pitavastatin magnesium in the amorphous form having water content less than about 2% wt/wt.

According to the process, amorphous form of pitavastatinmagnesium having water content less than about 2% wt/wt is prepared by contacting pitavastatinmagnesium containing about 8% to about 12% of water content with humid air in a fluidized bed apparatus.

In particular, the temperature is of about 25° C. to about 50° C., more particularly at about 30° C. to about 40° C. The contacting may be carried out, in particularly at about 6 hours to 2 days. As used herein, the term "humid" refers to a relative humidity of at least 30%. In particular, it may be at least about 50% and most particularly at least about 70%.

According to the further embodiment, there is provided substantially pure pitavastatinmagnesium in stable crystalline form.

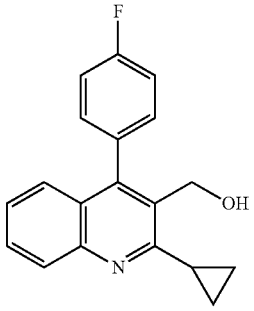
In another embodiment, there is provided pitavastatinmagnesium substantially free desfluoro impurity, cis-isomer impurity, pitavastatin 5-oxo impurity, pitavastatinlactone impurity, pitavastatin t-butyl diol ester impurity and pitavastatincondensed impurity when measured by area percentage

of HPLC. Also, pitavastatindiastereomeric impurity less than 0.3% by area percentage of HPLC.

According to the further embodiment, there is provided a pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatinmagnesium characterized by X-ray diffraction pattern having characteristic peaks at 2-theta values 10.1°, 13.2°, 19.3° and 27.2°±0.2°, and one or more pharmaceutically acceptable carriers, excipients or diluents.

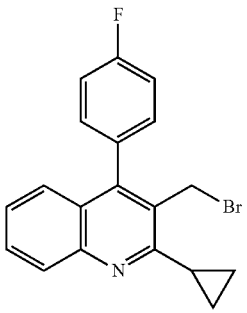
According to the further embodiment, there is provided a pharmaceutical composition comprising a therapeutically effective amount of amorphouspitavastatinmagnesium characterized by x-ray diffraction pattern substantially as depicted in FIG. **2**, and one or more pharmaceutically acceptable carriers, excipients or diluents.

The starting material, phosphonium bromide compound of Formula-IV, can be prepared from alcoholic compound of formula (VI)



(VI)

The alcoholic compound of formula (VI) is converted o phosphonium compound of Formula (IV) via formation of 3-(bromomethyl)-2-cyclopropyl-4(4'-fluorophenyl)quinoline of Formula (V) by the known process reported in the prior art. WO 95/11898 A1 in its reference example-7 and Example-1 or as per the process disclosed in U.S. Pat. No. 6,627,636 and U.S. Pat. No. 5,763,675.



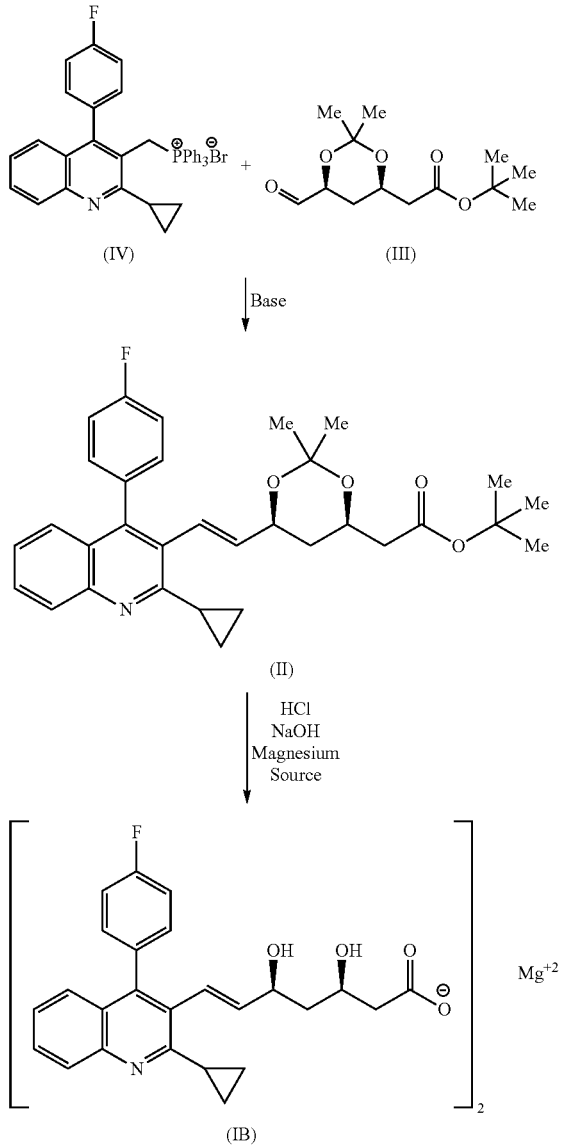
(V)

The bromo compound of formula (V) 3-(bromomethyl)-2-cyclopropyl-4-(4'-fluorophenyl)quinoline with wittig reagent like triphenyl phosphine in suitable non-polar solvents like toluene, o-xylene, chlorobenzeneetc to obtain phosphonium bromide compound of formula (IV).

The starting reagent, alcohol compound of formula (VI) can be prepared from the known process reported in the art like *Tetrahedron Letters*, Vol. 34, No. 51, p.p. 8271-8274 (1993); *Heterocycles*, Vol. 50, No. 1, 1999; *Drugs of Future* 1998 23 (8) or *Tetrahedron Asymmetry* 1993, Vol. 4, pp. 201-204 are reported herein as reference in its entirety.

As set forth in the following schemes, the pitavastatin magnesium can be prepared by as shown bellow:

Scheme-1



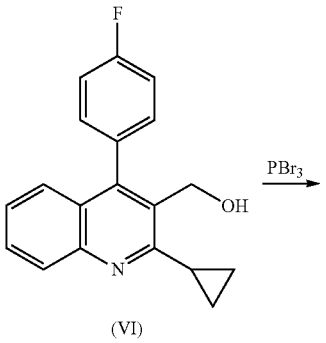
(IV) (III) (II) (IB)

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those

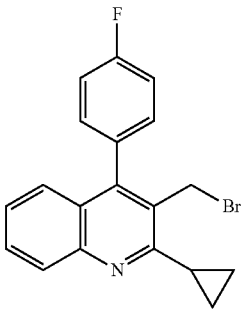
skilled in the art and are intended to be included within the scope of the present invention.

Preparation-1

Preparation of 3-(bromomethyl)-2-cyclopropyl-4-(4'-fluorophenyl)quinoline (V)



(VI)

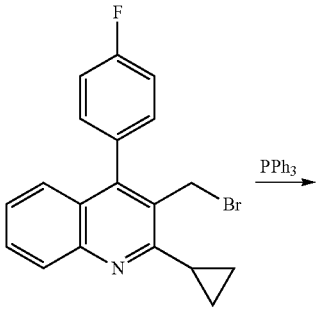


(V)

1 Kg of alcohol compound of formula (VI) and 8 L of methylene dichloride were taken in reactor at 0° C. 0.462 Kg of freshly prepared phosphonium bromide solution in 2 L methylene dichloride was added slowly and stirred at 25° C. for 2 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was quenched with 5% sodium bicarbonate solution to adjust the pH from 7-8. The organic layer was separated and washed with 5 L water followed by removal of solvent under vacuum at 45° C. The residue was treated with 2.5 L heptane at 60° C. and cooled to 15° C. The product was filtered at 15° C. and dried under vacuum at 55° C. for 8 hours to obtain 3-(bromomethyl)-2-cyclopropyl-4-(4'-fluorophenyl)quinoline.

Preparation-2

Preparation of Phosphonium Bromide Compound of Formula (IV)



(V)

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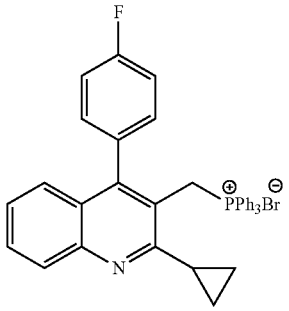
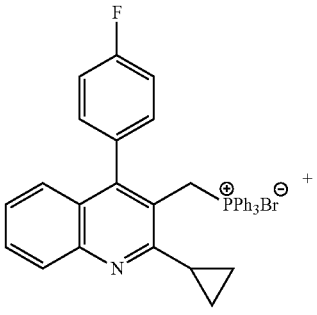


(IV)

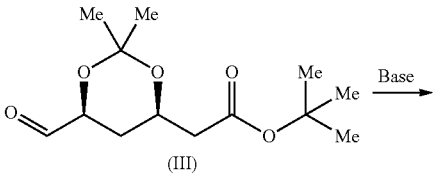
1 Kg of 3-(bromomethyl)-2-cyclopropyl-4-(4'-fluorophenyl)quinoline, 10 L of toluene and 300 mL of isopropanol were taken in reactor and heated at 50° C. 0.874 Kg of triphenyl phosphine solution in 2 L toluene was added slowly and stirred for 3 hours. The reaction mixture was cooled to 25° C. and stirred for 1 hour. The product was filtered and washed with toluene. The product was dried in tray dryer at 55° C. for 8 hours to obtain phosphonium bromide compound of formula (IV).

Example-1

Preparation of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester Compound of Formula II



(IV)



(III)

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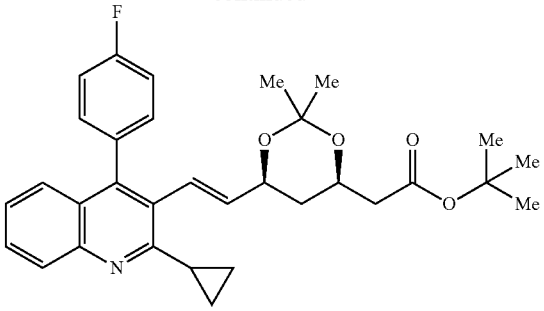


(II)

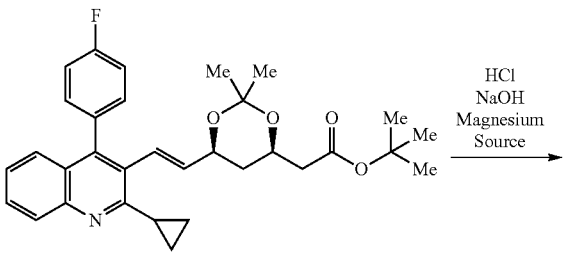
To the solution of 0.751 Kg of tert-butyl-2-((4R,6S)-6-formula-2,2-dimethyl-1,3-dioxan-4-yl)acetate (III) in 7 L of dimethylsulphoxide was added 1 Kg of phosphonium bromide compound of formula (IV) and 0.67 Kg of potassium carbonate. The reaction mixture was stirred at 25° C. for 10 hours. The reaction mixture was quenched with water and extracted with toluene. The organic layer was concentrated and the title compound was isolated using isopropanol as crude solid. The crude product thus obtained was recrystallized in methanol as shown below.

Purification of Olefin Compound of Formula II

Pitavastatin Olefin compound (II) (100 g) and methanol (600 mL) were heated to 60° C. to 65° C. to obtain the clear solution and stirred for 10 mins. Activated Carbon (10 g) were added at 60° C. to 65° C. and stirred for 10 min. The reaction mixture was filtered and washed with methanol (100 mL). The filtrate was cooled to 25° C. and gradually to 10° C. followed by stirring for 2 hours at 10° C. The resulting slurry was filtered and washed with chilled methanol (100 mL). The wet-cake was heated in methanol (480 mL) at 60° C. to 65° C. to obtain the clear solution. Activated Carbon (10 g) were added at 60° C. to 65° C. and stirred for 10 min. The reaction mixture was filtered and washed with methanol (100 mL). The filtrate was cooled to 25° C. and gradually to 10° C. followed by stirring for 2 hours at 10° C. The resulting slurry was filtered and washed with chilled methanol (100 mL). The wet-cake was dried under vacuum for 30 minutes followed by drying in hot air oven at 50° C. to 55° C. for 12 hours to obtain crystalline olefin compound (II) characterized by X-ray powder diffraction substantially as same as shown in FIG. **3** and DSC thermogram having endothermic peak at about 116.04° C. as shown in FIG. **4**.

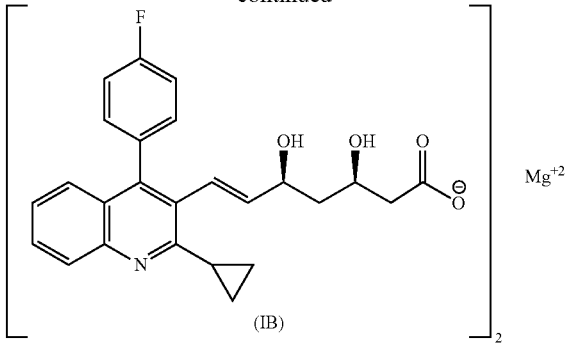
Example-2

Preparation of Pitavastatin Magnesium of Formula (IB)



(II)

-continued



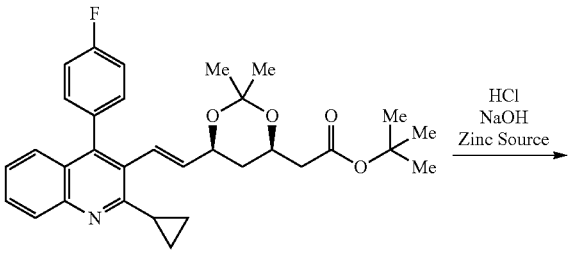
(IB)

To the solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula II (crystalline) in 1 L methanol was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution.

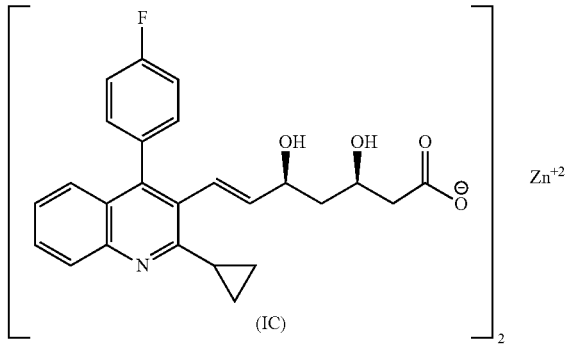
The reaction mixture was stirred for 4 hours at 25° C. and quenched in water. The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH of about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer is treated with 100 g of magnesium chloride hexahydrate and stirred for 30 min at 25° C. The solution is cooled to 15° C., filtered and washed with water. The product is dried in hot air oven for 4 hours to obtain 82 g of crystalline Pitavastatin Magnesium having water content of 11.0%. (XRD as shown in FIG. **1**)

Example-3

Preparation of Pitavastatin Zinc of Formula (IC)



(II)



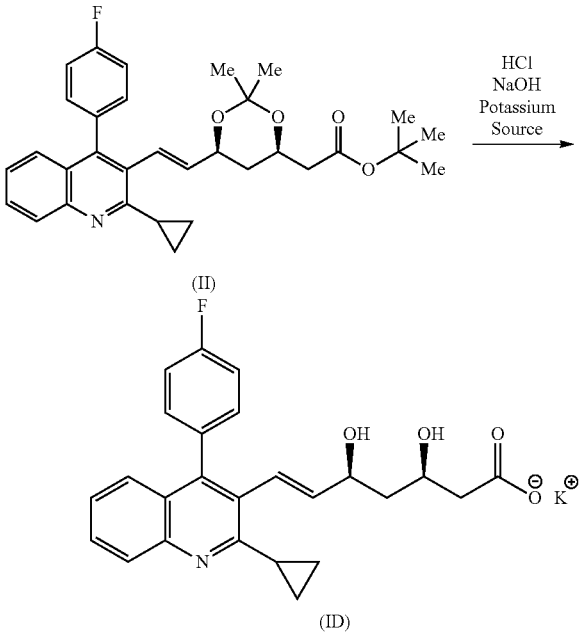
(IC)

To the solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-

1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula II (crystalline) in 1 L methanol was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution. The reaction mixture was stirred for 4 hours at 25° C. and quenched in water. The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH of about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer is treated with 100 g of zinc sulfate and stirred for 30 min at 25° C. The solution is cooled to 15° C., filtered and washed with water. The product is dried in hot air oven for 4 hours to obtain 75 g of crystalline Pitavastatin zinc.

Example-4

Preparation of Pitavastatin Potassium of Formula (ID)



To the solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula II (crystalline) in 1 L methanol was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution. The reaction mixture was stirred for 4 hours at 25° C. and quenched in water. The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH of about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer is treated with 80 g of Potassium hydroxide and stirred for 30 min at 25° C. The solution is cooled to 15° C., filtered and washed with water. The product is dried in hot air oven for 4 hours to obtain 72 g of crystalline Pitavastatin Potassium.

Example 5

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium was dissolved in 800 ml Ethyl Acetate by heating at 75° C. to 80° C. The slightly turbid solution was filtered through hyflow bed at 75° C. to 80° C. The filtrate was cooled to 25° C. and added to cyclohexane (3300 mL). The reaction mixture was stirred for 2 hours. The reaction mixture was filtered and wet-cake was washed with cyclohexane (100 mL). The product was dried in hot air oven for 12 hours to get 83.0 g amorphous Pitavastatin Magnesium. The obtained solid was amorphous as is shown by the X-ray diffraction pattern given in FIG. **2**.

Example 6

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium was dissolved in 800 ml Ethyl Acetate by heating at 75° C. to 80° C. The slightly turbid solution was filtered through hyflow bed at 75° C. to 80° C. The filtrate was distilled under vacuum till dry powder obtained at 45° C. to 50° C. The solid was cooled to 25° C. and cyclohexane (500 mL) was added to the filtrate and stirred for 30 min. The reaction mixture was filtered and wet-cake was washed with cyclohexane (100 mL). The product was dried in hot air oven for 12 hours to get 83.0 g amorphous Pitavastatin Magnesium. The obtained solid was amorphous as is shown by the X-ray diffraction pattern given in FIG. **2**.

Example 7

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium and Methanol (500 mL) were stirred in RBF for 30 minutes. The reaction mixture was distilled at 45° C. to 50° C. under vacuum to obtain dry product. The filtrate was distilled under vacuum till dry powder obtained at 45° C. to 50° C. The solid was cooled to 25° C. and cyclohexane (500 mL) was added to the filtrate and stirred for 30 min. The reaction mixture was filtered and wet-cake was washed with cyclohexane (100 mL). The product was dried in hot air oven for 12 hours to get 83.0 g amorphous Pitavastatin Magnesium.

Example 8

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium was dissolved in 800 ml Acetone by heating at 55° C. to 60° C. The slightly turbid solution was filtered through hyflow bed at 55° C. to 60° C. The filtrate was cooled to 25° C. and added to diisopropyl ether (3000 mL). The reaction mixture was stirred for 3-min. The reaction mixture was filtered and wet-cake was washed with diisopropyl ether (100 mL). The product was dried in hot air oven for 12 hours to get 45.0 g amorphous Pitavastatin Magnesium.

Example 9

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of Pitavastatin Magnesium having water content 11% was dried in fluid bed dried at 45° C. for 2 days to obtain

amorphous Pitavastatin Magnesium having water content less than 2% wt/wt. An X-ray diffraction study on the product showed it to be amorphous.

Example 10

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of Pitavastatin Magnesium having water content 11% was dried in vacuum tray dryer at about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of 24 hours to obtain amorphous Pitavastatin Magnesium having water content less than 2% wt/wt. An X-ray diffraction study on the product showed it to be amorphous, see FIG. **2**.

While the present invention has been described in terms of its specific embodiments, certainmodifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Advantages of the Invention

1. The present invention provides novel pharmaceutically acceptable salt of alkali metal salts of Pitavastatin.

2. The present invention provides an improved process for the preparation of pitavastatinalkali metal salts.

3. The present invention provides crystalline form of pitavastatinmagnesium having 8% to 12% water content.

4. The present invention also provides amorphous form of pitavastatinmagnesium and process for preparation thereof.

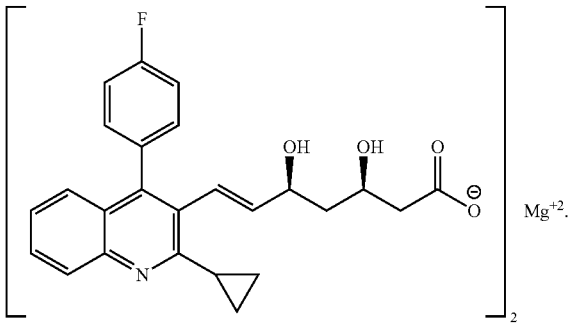
5. The present invention provides amorphous form of pitavastatinmagnesium containing less than about 2% of water content.

6. The process provided is eco-friendly, economically viable and easily scalable on large scale production.

We claim:

1. An isolated pitavastatin magnesium compound of Formula (IB) or a hydrate thereof

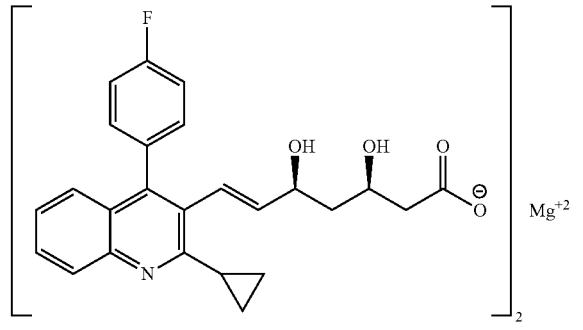
(IB)



2. The compound as claimed in claim **1**, wherein the compound has a water content in the range of from about 7% to about 12% wt/wt.

3. A crystalline pitavastatin magnesium compound of Formula (IB) or a hydrate thereof

(IB)



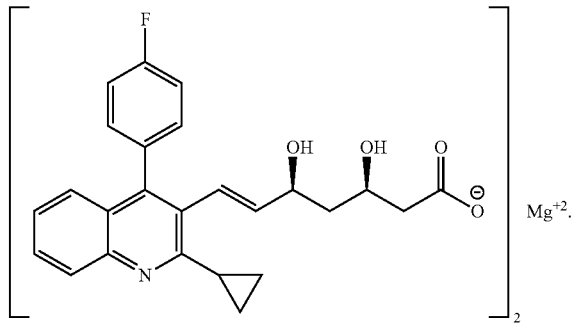
wherein the crystalline pitavastatin magnesium compound has an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ (±0.2° 2θ) at 10.1°, 13.2°, 19.3° and 27.2°±0.2°.

4. The compound as claimed in claim **3** having an x-ray powder diffraction pattern substantially same as that shown in FIG. **1**.

5. The compound as claimed in claim **2**, wherein the compound is amorphous.

6. An amorphous pitavastatin magnesium compound of Formula (IB) or a hydrate thereof having an x-ray powder diffraction pattern substantially the same as that shown in FIG. **2**

(IB)



7. The compound as claimed in claim **5**, wherein the compound has a water content less than about 5% wt/wt.

8. The compound as claimed in claim **5** having a specific optical rotation of about +22.0 to +22.5 in 1% DMSO at 20±0.5° C.

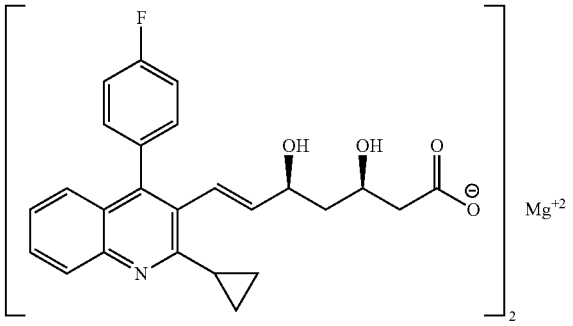
9. A pharmaceutical composition comprising pitavastatin magnesium of claim **5** and one or more pharmaceutically acceptable carriers or excipients.

10. The compound as claimed in claim **5**, wherein the pitavastatin magnesium is substantially pure having purity greater than about 99% by area percentage of HPLC.

11. The compound as claimed in claim **5**, wherein the pitavastatin magnesium is substantially pure having less than about 0.3% of diastereomeric impurity by area percentage of HPLC.

12. A process for the preparation of pitavastatin magnesium of Formula (IB) as claimed in claim **5**,

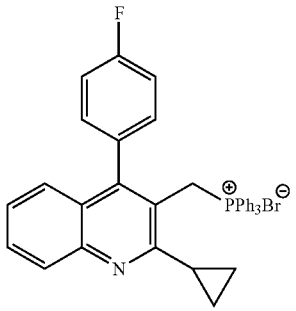
(IB)



the process comprising:

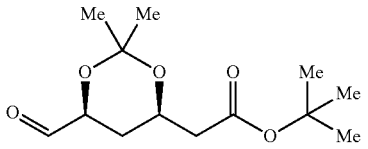
(a) reacting phosphonium bromide compound of Formula-IV

(IV)



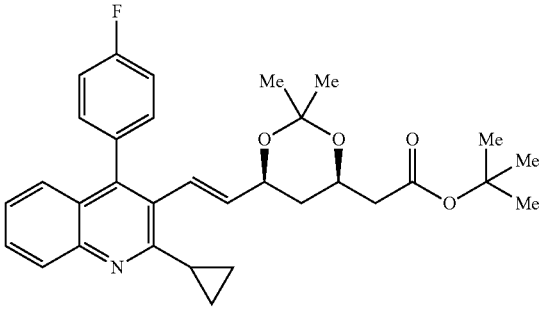
with an aldehyde compound of Formula-III

(III)



in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvents to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl) quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of Formula-II;

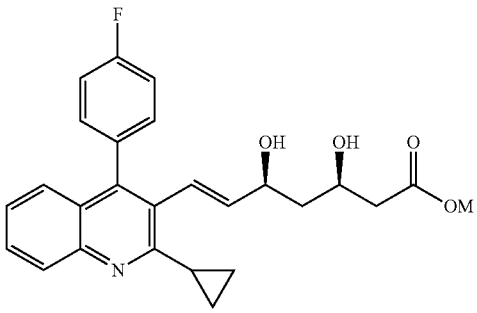
(II)



(b) hydrolyzing the compound of Formula-II under acidic conditions to remove acetonide protection to form a diol compound;

(c) treating the diol compound of step (b) in situ with an alkali metal hydroxide to form corresponding alkali metal salt of pitavastatin (I);

(I)



wherein, M is Na^+, K^+, Li^+;

(d) treating alkali metal salt of pitavastatin (I) with a magnesium source to obtain pitavastatin magnesium; and

(e) isolating the pitavastatin magnesium.

13. The process as claimed in claim **12**, wherein in step (a) the alkali or alkaline earth metal base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, and cesium carbonate.

14. The process as claimed in claim **12**, wherein in step (a) the suitable polar aprotic solvent comprises one or more of dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methylpyrrolidone, or mixtures thereof.

15. The process as claimed in claim **12**, wherein the compound (II) can optionally be isolated by removal of the solvent.

16. The process as claimed in claim **12**, wherein the compound (II) can optionally be purified in a suitable polar solvent selected from methanol, ethanol, isopropanol, acetone, DMF, ethyl acetate, or butyl acetate.

17. The process as claimed in claim **12**, wherein in step (b) the hydrolysis of compound (II) under acidic conditions can be done by selecting suitable acids from hydrochloric acid, acetic acid, sulfuric acid, nitric acid, and phosphoric acid.

18. The process as claimed in claim **12**, wherein in step (c) the alkali metal hydroxide comprises one or more of sodium hydroxide, potassium hydroxide, and lithium hydroxide.

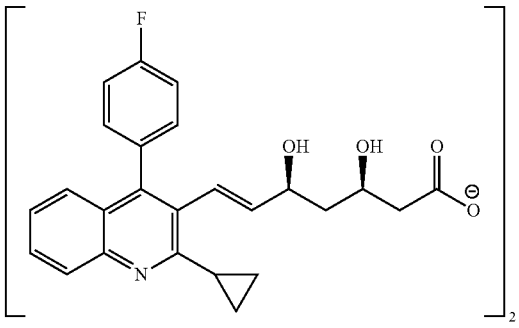
19. The process as claimed in claim **15**, wherein in step (c) the alkali metal salt of pitavastatin is pitavastatin sodium.

20. The process as claimed in claim **12**, wherein in step (d) the magnesium source comprises one or more of magnesium chloride, magnesium methoxide, magnesium acetate and hydrates thereof.

21. The process as claimed in claim **15**, wherein in step (e) the pitavastatin magnesium is isolated in a crystalline form.

22. A crystalline pitavastatin magnesium compound of Formula (IB) or a hydrate thereof,

(IB)



wherein the pitavastatin magnesium compound has an X-ray powder diffraction pattern having characteristics peaks expressed in degrees 2θ (±0.2° 2θ) at 10.1°, 13.2°, 19.3° and 27.2°±0.2° and is characterized by one or more of:

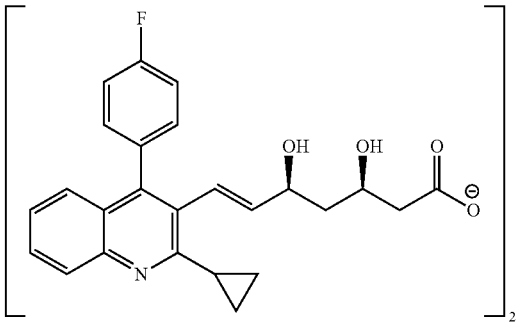
(a) having a specific optical rotation of about +22.0 to +22.5 in 1% DMSO at 20±0.5° C.;

(b) having a purity greater than about 99% by area percentage of HPLC; and

(c) having less than about 0.3% of diastereomeric impurity by area percentage of HPLC.

23. A pitavastatin magnesium compound of Formula (IB) or a hydrate thereof,

(IB)



wherein

the pitavastatin magnesium compound is crystalline and has an X-ray powder diffraction pattern having characteristics peaks expressed in degrees 2θ (±0.2° 2θ) at 10.1°, 13.2°, 19.3° and 27.2°±0.2°; or

the pitavastatin magnesium compound is crystalline and has an x-ray powder diffraction pattern substantially same as that shown in FIG. **1**; or

the pitavastatin magnesium compound is amorphous and has an x-ray powder diffraction pattern substantially the same as that shown in FIG. **2**.

24. The compound as claimed in claim **23**, wherein the compound is crystalline and has a water content in the range of from about 7% to about 12% wt/wt.

25. The compound as claimed in claim **23**, wherein the compound is amorphous and has a water content less than about 5% wt/wt.

26. The compound as claimed in claim **23**, having a specific optical rotation of about +22.0 to +22.5 in 1% DMSO at 20±0.5° C.

27. The compound as claimed in claim **23**, wherein the pitavastatin magnesium is substantially pure having a purity greater than about 99% by area percentage of HPLC.

28. The compound as claimed in claim **23**, wherein the pitavastatin magnesium is substantially pure having less than about 0.3% of diastereomeric impurity by area percentage of HPLC.

29. A pharmaceutical composition comprising the pitavastatin magnesium of claim **23** and one or more pharmaceutically acceptable carriers or excipients.

30. The compound as claimed in claim **6**, wherein the amorphous pitavastatin magnesium compound has a water content less than about 5% wt/wt.

* * * * *

EXHIBIT E

US009034901B2

(12) **United States Patent**
Dwivedi et al.

(10) **Patent No.: US 9,034,901 B2**
(45) **Date of Patent: May 19, 2015**

(54) **PITAVASTATIN CALCIUM AND PROCESS FOR ITS PREPARATION**

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(73) Assignee: **Cadila Healthcare Limited**, Ahmedabad (IN)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/818,681**

(22) PCT Filed: **Aug. 24, 2011**

(86) PCT No.: **PCT/IN2011/000571**

§ 371 (c)(1),
(2), (4) Date: **May 8, 2013**

(87) PCT Pub. No.: **WO2012/025939**

PCT Pub. Date: **Mar. 1, 2012**

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US 2014/0148481 A1 May 29, 2014

(30) **Foreign Application Priority Data**

Aug. 25, 2010 (IN) 2374/MUM/2010

(51) **Int. Cl.**
C07D 215/14 (2006.01)

(52) **U.S. Cl.**
CPC ***C07D 215/14*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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European Patent Office Acting as The International Preliminary Examining Authority, International Preliminary Report on Patentability, PCT/IN2011/000571, Jan. 19, 2012.

Primary Examiner — Timothy R Rozof

(74) *Attorney, Agent, or Firm* — Brij Khera; William D. Hare; McNeely, Hare & War, LLP

(57) **ABSTRACT**

The invention provides the process for the preparation of pitavastatin and its pharmaceutically acceptable salts thereof. In particular, the invention provides a process for the preparation of stable pitavastatin calcium in crystalline form having water content less than 5% wt/wt. The present invention also provides stable crystalline form of pitavastatin calcium substantially free from crystal Form-A and use thereof for pharmaceutical compositions.

32 Claims, 5 Drawing Sheets

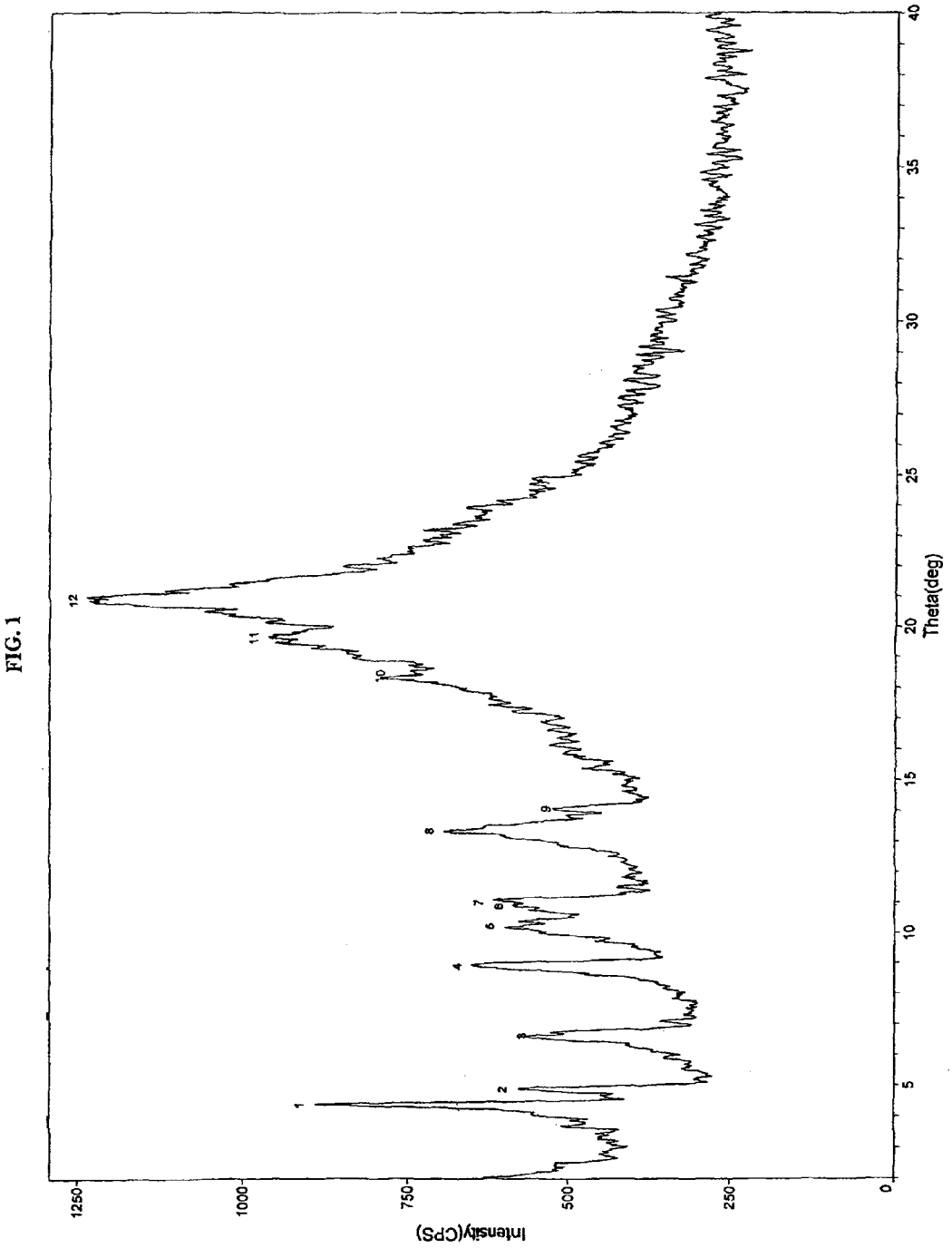
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FIG. 1

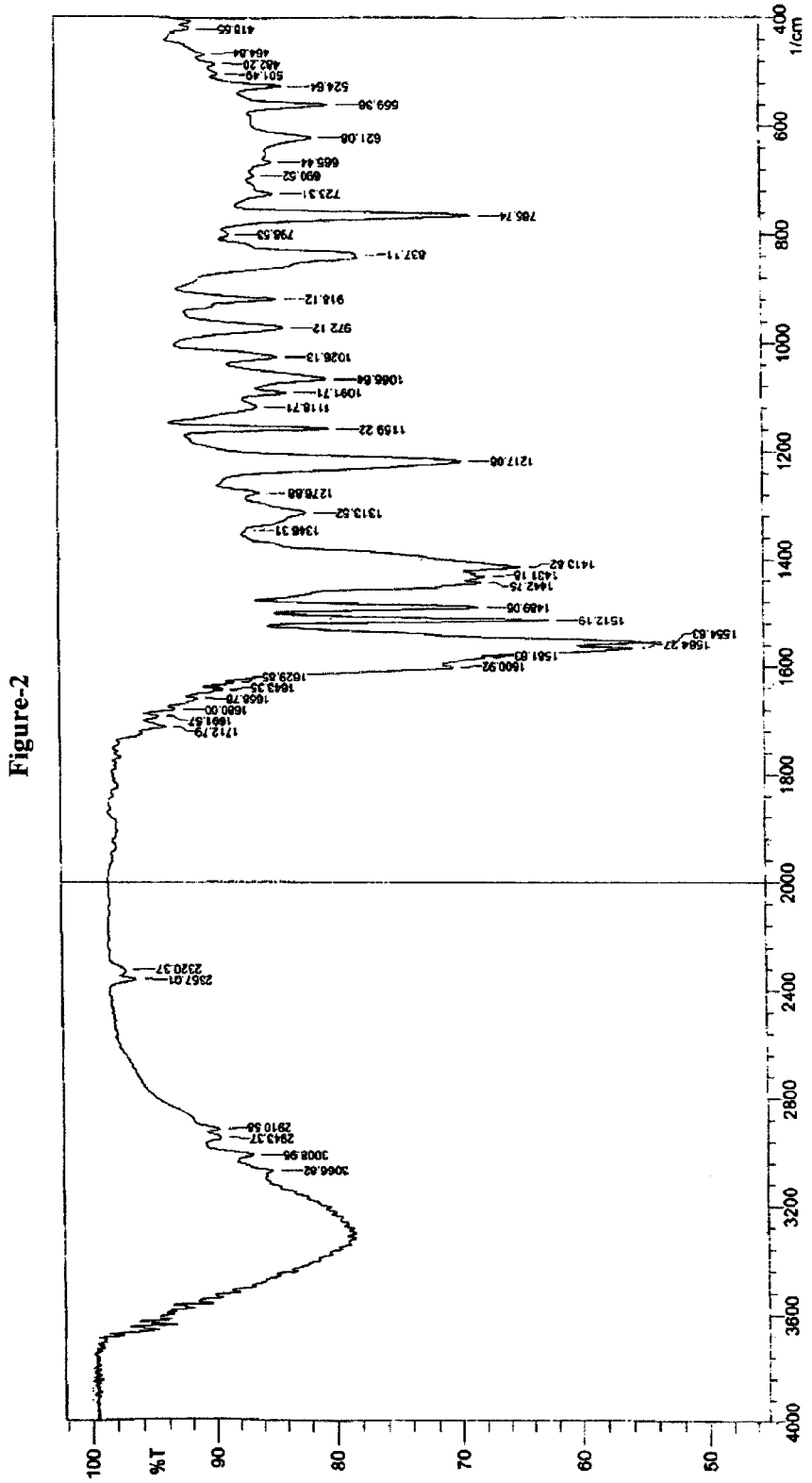
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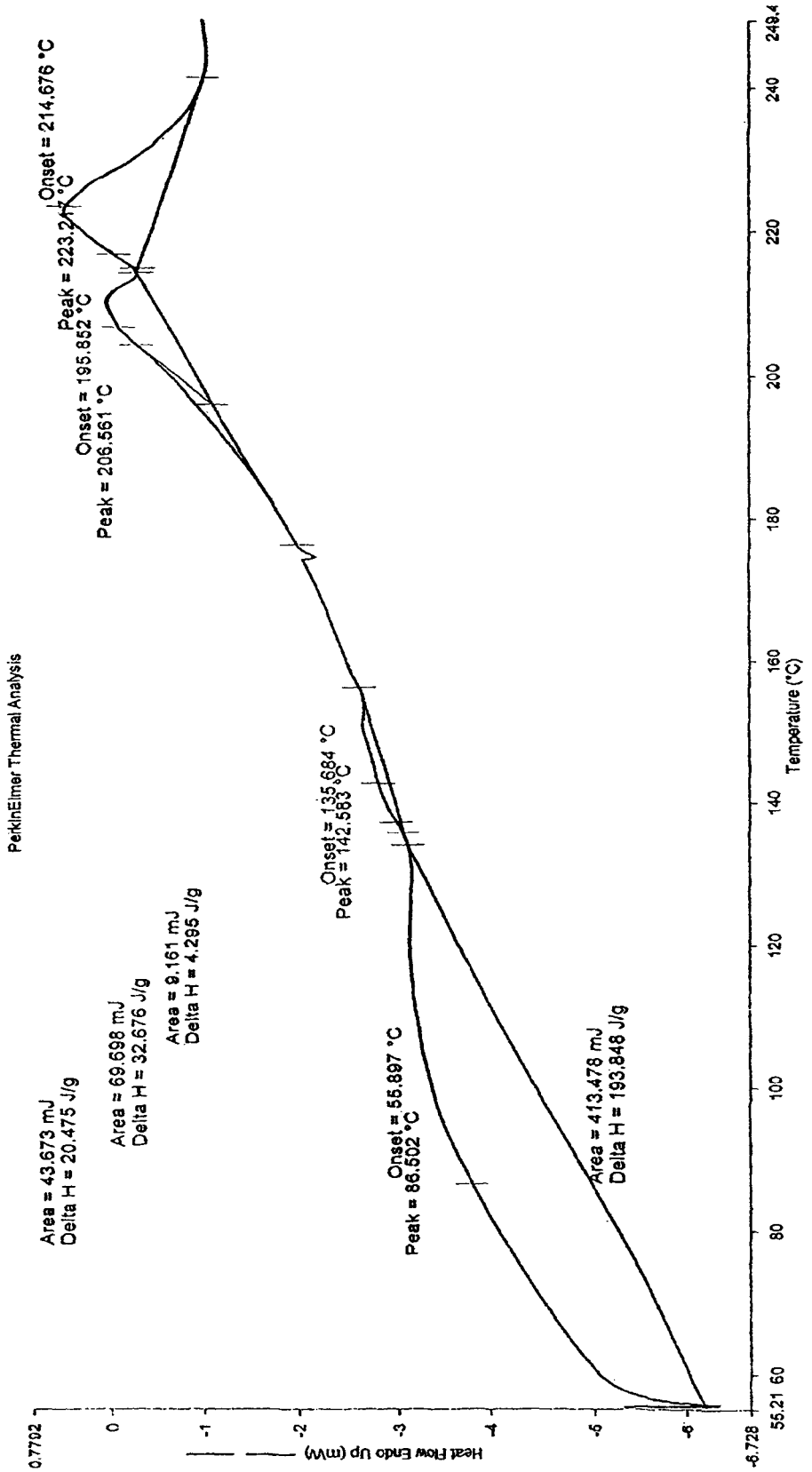
Figure-2

FIG. 3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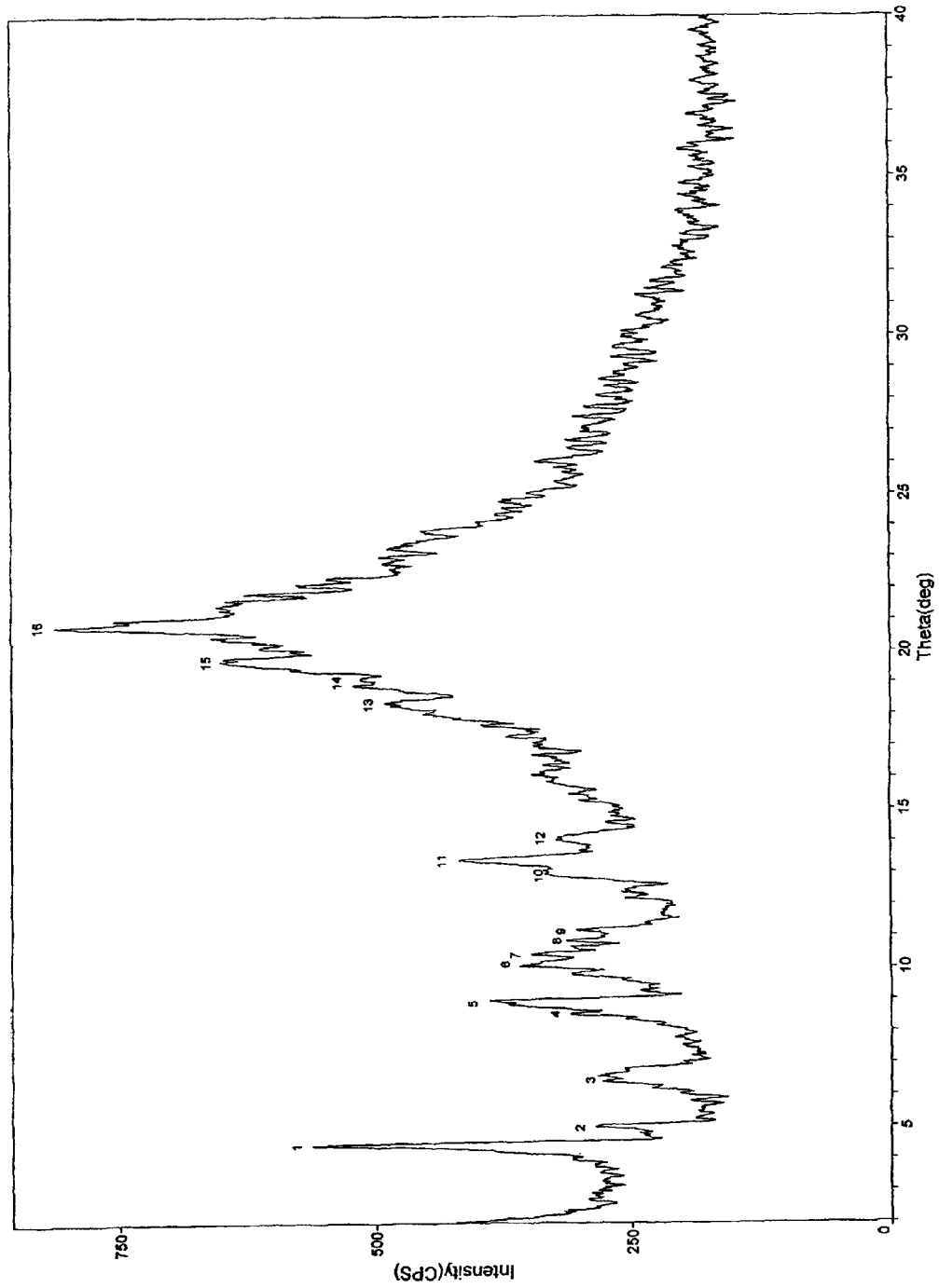
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FIG. 4

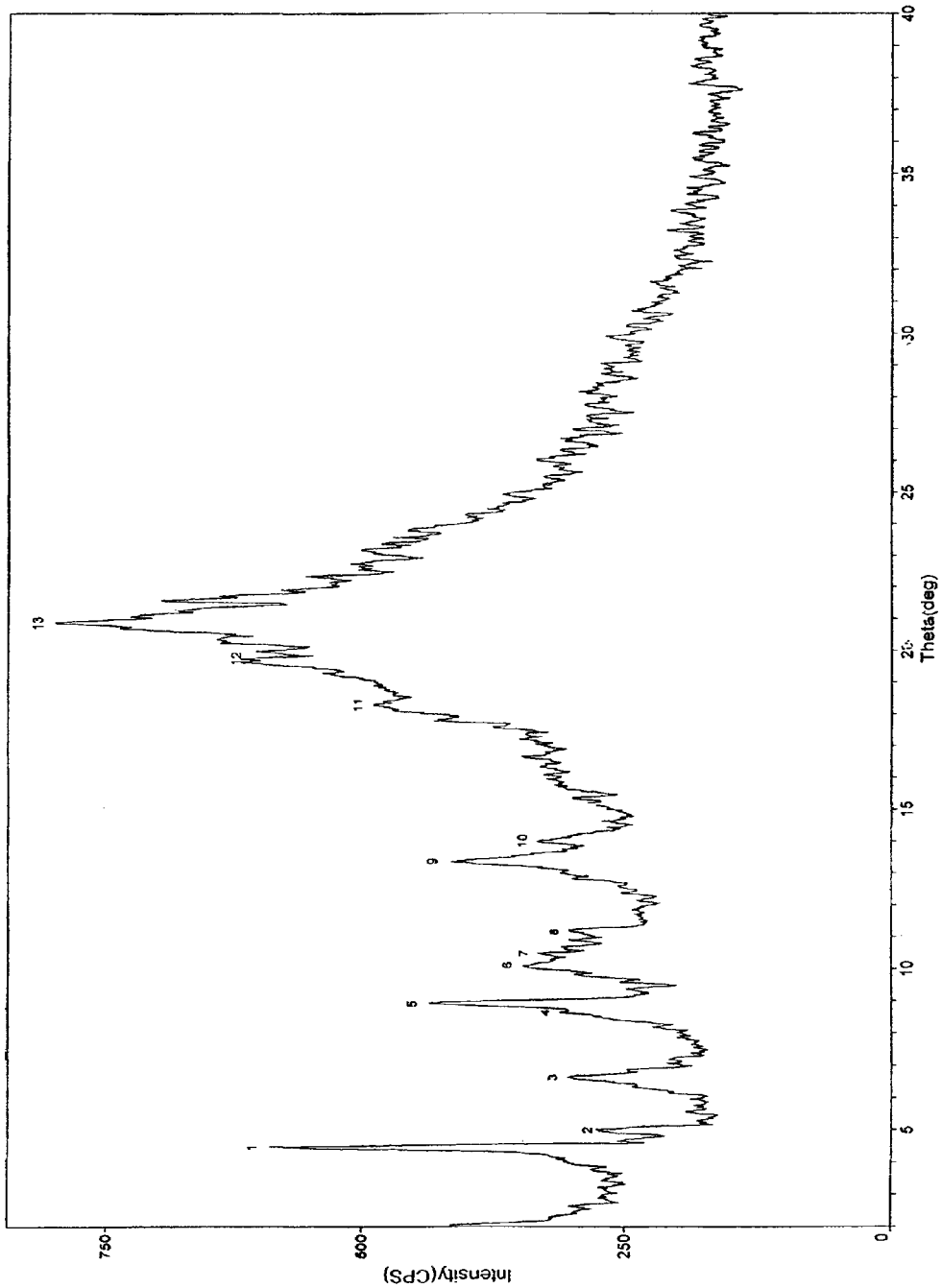
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FIG. 5

PITAVASTATIN CALCIUM AND PROCESS FOR ITS PREPARATION

FIELD OF THE INVENTION

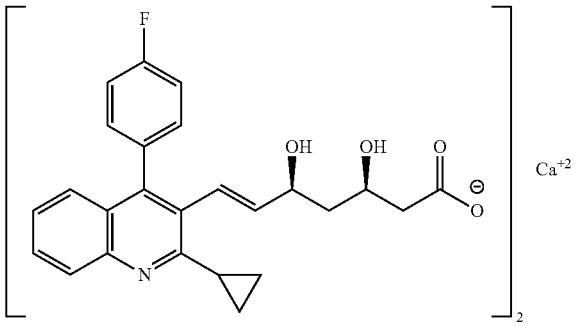
The invention relates to processes for the preparation of pitavastatin and its pharmaceutically acceptable salts thereof. In particular, the invention relates to a process for the preparation of stable pitavastatin calcium in crystalline form having water content less than 5% wt/wt. More particularly, the present invention relates to a stable crystalline form of pitavastatin calcium substantially free from crystal Form-A. The invention also relates to crystalline pitavastatin calcium and pharmaceutical compositions that include the crystalline pitavastatin calcium.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Pitavastatin calcium is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-flourophenyl)-quinolin-3-yl]-3,5-dihydroxy-6-(E)-heptenoic acid calcium salt having the Formula I is known in the literature.

(I)



Pitavastatin is a synthetic lipid-lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase (HMG-CoA Reductase inhibitor). This enzyme catalyzes the conversions of HMG-CoA to mevalonate, inhibitors are commonly referred to as "statins". Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. Pitavastatin is used in the treatment of hyperchloesterolemia and mixed dyslipidemia.

Pitavastatin calcium has recently been developed as a new chemically synthesized and powerful statin by Kowa Company Ltd, Japan. On the basis of reported data, the potency of pitavastatin is dose-dependent and appears to be equivalent to that of atorvastatin. This new statin is safe and well tolerated in the treatment of patients with hypercholesterolaemia.

Significant interactions with a number of other commonly used drugs can be considered to be extremely low.

Processes for the preparation of pitavastatin are described in EP-A-0304063 and EP-A-1099694 and in the publications by N. Miyachi et al. in *Tetrahedron Letters* (1993) vol. 34, pages 8267-8270 and by K. Takahashi et al. in *Bull. Chem. Soc. Japan* (1995) Vol. 68, 2649-2656. These publications describe the synthesis of pitavastatin in great detail but do not describe the hemi-calcium salt of pitavastatin. The publications by LA. Sorbera et al. in *Drugs of the Future* (1998) vol. 23, pages 847-859 and by M. Suzuki et al. in *Bioorganic & Medicinal Chemistry Letters* (1999) vol. 9, pages 2977-2982 describe pitavastatin calcium, however, a precise procedure for its preparation is not given. A full synthetic procedure for the preparation of pitavastatin calcium is described in EP-A-0520406. In the process described in this patent, pitavastatin calcium is obtained by precipitation from an aqueous solution as a white crystalline material with a melting point of 190-192° C.

US 2009/0182008 A1 discloses various polymorphic forms A, B, C, D, E, and F, and the amorphous form of pitavastatin calcium salt (2:1). In particular, the crystalline Form A having water content from about 5% to about 15% and process for its preparation are disclosed.

US 2009/0176987 A1 ("the US '987 A1) also discloses polymorphic form crystal form A of pitavastatin calcium which contains from 5 to 15% of water and which shows, in its X-ray powder diffraction as measured by using CuKα radiation, a peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

The US '987 A1 discloses that pitavastatin calcium (Crystal Form-A) when subjected to drying in a usual manner, the crystallinity decreases to a state which is close to an amorphous state and is shown by X-ray powder diffraction pattern as shown in FIG. **2** when the water content becomes about 4%. It is also disclosed that even the crystallinity decreases close to an amorphous state for compound having X-ray powder diffraction pattern as shown in FIG. **1** prior to the drying. It is also disclosed that the stability of crystal Form-A and crystallinity has a very close relationship with respect to water content. Further, it has been reported that the pitavastatin calcium, which has become amorphous, has very poor stability during the storage, as shown in Table. 1.

Table.1 of the US '987 A1 also shows that pitavastatin calcium kept at 40° C. (air tight) has water content of about 7.89 (initial) and 7.81 (after 90 days) with total impurities 0.179 (initial) and 0.211 (after 90 days) with purity of 99.38% (Initial) and 99.64 (after 90 days). Contradictorily, it shows reports that pitavastatin calcium kept in open air has water content of about 7.89 (initial) and 1.77 (after 90 days) with total impurities 0.179 (initial) and 2.099 (after 90 days) with purity of 99.38% (Initial) and 96.49 (after 90 days).

The US '987 A1 also discloses that stability of pitavastatin calcium can be remarkably improved by controlling the water content in the drug substance within a specific range. Also, it reports that there are three types of crystal forms having the same water content range i.e. Crystal Form-A, Crystal Form-B and Crystal Form-C. It has been found that among the three crystalline forms, crystal Form-A is most preferred as a drug substance for pharmaceuticals.

Crystal Form-A is having water content in the range of 5% to 15%, preferably from 9% to 11%. It also discloses that Crystal Form-A is the best as a drug substance for pharmaceuticals.

International (PCT) Publication No. WO 2007/132482 A1 discloses a process for the preparation of pitavastatin calcium by condensing bromide salt of Formula-3 with aldehyde compound of Formula-4 to obtain olefinic compound of Formula-5 and converting olefinic compound to pitavastatin calcium via organic amine salt for purification.

International (PCT) Publication No. WO 2010/089770 A2 discloses a process for the preparation of pitavastatin calcium. WO 2011/089623 A2 discloses alkali or alkaline earth metal salts of pitavastatin.

Polymorphism is defined as the ability of a substance to crystallize in more than one crystal lattice arrangement. Polymorphism can influence many aspects of solid state proper-

ties of a drug. Different crystal modifications of a substance may differ considerably from one another in many respects such as their solubility, dissolution rate and finally bioavailability. An exhaustive treatment of polymorphism in pharmaceutical and molecular crystals is given e.g. by Byrn (Byrn, S. R., Pfeiffer, R. R., Stowell, J. G., "Solid-State Chemistry of Drugs", SSCI Inc., West Lafayette, Ind., 1999), Brittain, H. G., "Polymorphism in Pharmaceutical Solids", Marcel Decker, Inc., New York, Basel, 1999) or Bernstein (Bernstein, J., "Polymorphism in Molecular Crystals", Oxford University Press, 2002).

In view of the above, it is therefore, desirable to provide an efficient more economical, less hazardous and eco-friendly process for the preparation of highly pure stable pitavastatin calcium having water content less than 5% wt/wt. The crystalline form provided herein is at least stable under ordinary stability conditions with respect to purity, storage and is free flowing powder. The process is simple, cost-effective, eco-friendly and commercially viable.

SUMMARY OF THE INVENTION

In one general aspect there is provided storage stable pitavastatin calcium in crystalline form having water content less than about 5% wt/wt.

In another general aspect there is provided a stable pitavastatin calcium in crystalline form characterized by X-ray powder diffraction peaks at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ) and having water content less than about 5% wt/wt.

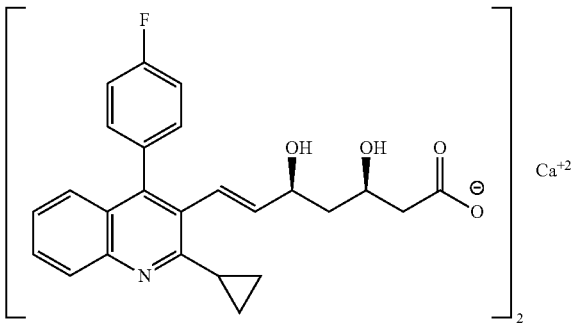
In another general aspect there is provided a stable pitavastatin calcium which is substantially free from crystal Form-A and doesn't show an X-ray powder diffraction peak having relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°. In another general aspect there is provided a process for the preparation of a stable crystalline form of pitavastatin calcium having water content less than about 5% wt/wt, the process comprising:

a) obtaining a solution of pitavastatin calcium in one or more solvents; and

b) isolating the crystalline pitavastatin calcium optionally, in presence of one or more of anti-oxidants.

In further aspect, there is provided a process for the preparation of stable pitavastatin calcium of Formula I

(I)



having water content less than 5% wt/wt and characteristic peak in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ)

the process comprising:

(a) reacting the phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in presence of an alkali or alkaline earth metal bases in one or more of suitable solvent to provide an olefin compound of Formula-II,

(b) hydrolyzing the olefinic compound of Formula-II by subjecting under the acidic conditions to remove the acetonide and form diol compound, which upon treating with an alkali metal hydroxide base to form the corresponding alkali metal salt of pitavastatin (Ia);

(c) treating alkali metal salt of pitavastatin with a calcium source to obtain pitavastatin calcium (I);

(d) obtaining a solution of pitavastatin calcium in one or more solvents; and

(e) isolating the crystalline pitavastatin calcium optionally, in the presence of one or more anti-oxidants.

According to the further aspect, there is provided a process for the preparation of pitavastatin calcium in stable crystalline form having water content less than about 5% wt/wt,

the process comprising:

(a) providing pitavastatin calcium in crystalline form having water content in the range of 8% to 12%;

(b) contacting pitavastatin calcium with humid air in a fluidized bed drier, or maintaining the pitavastatin calcium at a temperature of from about 5° to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 to 5 days;

(c) recovering pitavastatin calcium in crystalline form having water content less than 5% wt/wt; and

(d) stabilizing crystalline pitavastatin calcium by packing under controlled condition.

In further aspect, there is provides a process for stabilizing crystalline pitavastatin calcium having water content less than about 5% wt/wt and characteristic peak in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ), the process comprising:

(a) placing crystalline pitavastatin calcium under nitrogen atmosphere in a double polythene bag or non-permeable bag tied with a thread;

(b) placing the bag of step (a) inside a black color polyethylene bag, optionally containing oxygen busters and sealing it;

(c) placing the bag of step (b) inside a triple laminated bag, optionally containing oxygen busters and sealing it; and

(d) placing the sealed triple laminated bag inside a high density polyethylene (HDPE) container, sealing it and storing in a controlled environment chamber from about 25° C. to about 40° C.

According to the further aspect, there is provided substantially pure pitavastatin calcium in stable crystalline form.

In another aspect, the present invention accordingly provides a pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatin calcium having water content of less than about 5% and one or more pharmaceutically acceptable carriers, excipients or diluents.

An aspect of the present application provides A pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatin calcium having water content less than about 5% and substantially free from one or more of its corresponding impurities as measured by HPLC.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. **1**: X-ray diffraction pattern of crystalline pitavastatin calcium as per process of present invention.

FIG. **2**: IR spectra of crystalline pitavastatin calcium as per process of present invention.

FIG. **3**: Differential Scanning Calorimetry analysis of crystalline pitavastatin calcium as per process of present invention.

FIG. **4**: X-ray diffraction pattern of stable crystalline pitavastatin calcium after exposure to a relative humidity of 75% at 40° C. for a period of at least three months.

FIG. **5**: X-ray diffraction pattern of stable crystalline pitavastatin calcium after exposure to a relative humidity of 60% at 25° C. for a period of at least three months.

DETAILED DESCRIPTION ON THE INVENTION

The prior art discloses the use of organic amine salts of pitavastatin for obtaining better purity. The present inventors have found that pitavastatin calcium prepared by using the process provided herein provides better yield and purity and avoids the use of amine salt formation. This significantly improves the process economics and commercial viability.

The present invention can comprise (open ended) or consist essentially of the components of the present invention as well as other ingredients or elements described herein. As used herein, "comprising" means the elements recited, or their equivalent in structure or function, plus any other element or elements which are not recited. The terms "having" and "including" are also to be construed as open ended unless the context suggest otherwise.

As used here in the term "isolation" may include filtration, filtration under vacuum, centrifugation, and decantation. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

All ranges recited herein include the endpoints, including those that recite a range "between" two values. Terms such as "about", "general", "substantially" and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

The term "substantially pure" means stable pitavastatin calcium containing less than about 0.15% (wt/wt) any single individual impurities like desflouro impurity, cis-isomer impurity, pitavastatin 5-oxo impurity, pitavastatin Lactone impurity, pitavastatin t-butyl diol ester impurity, and pitavastatin condensed by area percentage of HPLC or containing less than about 0.3% (wt/wt) pitavastatin diastereomeric impurity and pitavastatin enantiomeric impurity.

The term "controlled conditions" refers to packing under nitrogen atmosphere and in a double polythene bag or non-permeable bag tied with a thread, keeping primary packing containing crystalline pitavastatin calcium inside a black color polyethylene bag optionally containing oxygen busters and sealing it, placing above the double polyethylene bag or non-permeable bag inside a triple laminated bag optionally containing oxygen busters and sealing it, and placing the sealed triple laminated bag inside a closed high density polyethylene (HDPE) container and storing in controlled environment chamber at about 25° C. to about 40° C.

The term "suitable solvent" means a single or a combination of two or more solvents.

In one general aspect, there is provided storage stable pitavastatin calcium in crystalline form having water content less than about 5% wt/wt.

In another general aspect, there is provided stable pitavastatin calcium in crystalline form characterized by X-ray powder diffraction peaks at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ) and having X-ray powder diffraction pattern as shown in FIG. **1**.

According to an aspect, the present invention provides stable pitavastatin calcium (1), which is substantially free from crystal Form-A characterized by X-ray powder diffraction having a peak of relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

Herein the term "substantially free from crystal Form-A" means less than about 1%, particularly less than 0.1%, more particularly not in detectable amount of crystal Form-A, as appropriate or in the case of crystalline solids.

As used herein, "stable pitavastatin calcium" includes either of the following:

(a) pitavastatin calcium is substantially free from crystal Form-A and doesn't show an X-ray powder diffraction peak having relative intensity of more than 25% at a diffraction angle (2θ) of 30.16° after storage for 3 months at 40° C. and a relative humidity of 75%, or

(b) pitavastatin calcium is substantially free from crystal Form-A and doesn't show an X-ray powder diffraction peak having relative intensity of more than 25% at a diffraction angle (2θ) of 30.16° after storage for 3 months at 25° C. and a relative humidity of 60%, or

(c) pitavastatin calcium containing less than about 0.15% (wt/wt) any single individual impurities like desflouro impurity, cis-isomer impurity, pitavastatin 5-oxo impurity, pitavastatin lactone impurity, pitavastatin t-butyl diol ester impurity, and pitavastatin condensed by area percentage of HPLC after storage for 3 months at 40° C. and a relative humidity of 75%, or

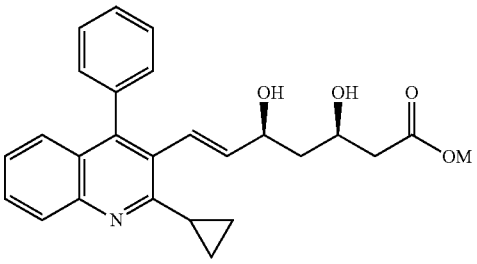
(d) pitavastatin calcium containing less than about 0.15% (wt/wt) any single individual impurities like desflouro impurity, cis-isomer impurity, pitavastatin 5-oxo impurity, pitavastatin lactone impurity, pitavastatin t-butyl diol ester impurity, and pitavastatin condensed by area percentage of HPLC after storage for 3 months at 25° C. and a relative humidity of 60%, or

(e) crystalline pitavastatin calcium that after exposure to a relative humidity of 75% at 40° C. for a period of at least three months does not have water content greater than 5% wt/wt, or

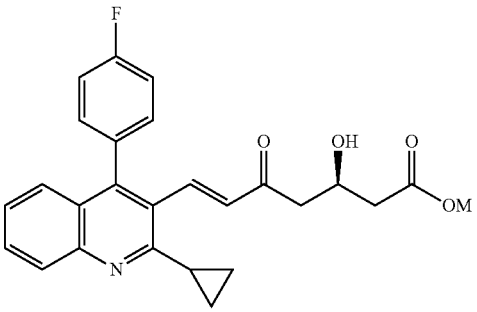
(f) crystalline pitavastatin calcium that after exposure to a relative humidity of 75% at 40° C. for a period of at least three months does not show a peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

The above impurities are present in the preparation of pitavastatin calcium includes the following which were determined from an HPLC analysis of different batches of pitavastatin calcium produced by the process described in the specification herein after, and identified below in the scheme-1.

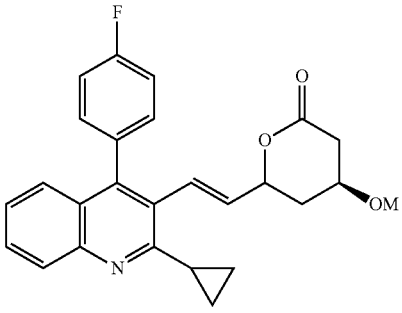
Scheme-1



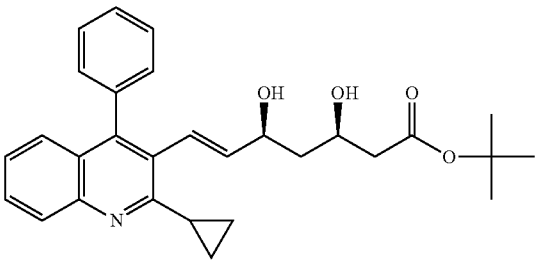
Des-Flouro Pitavastatin



Pitavastatin 5-oxo Impurity

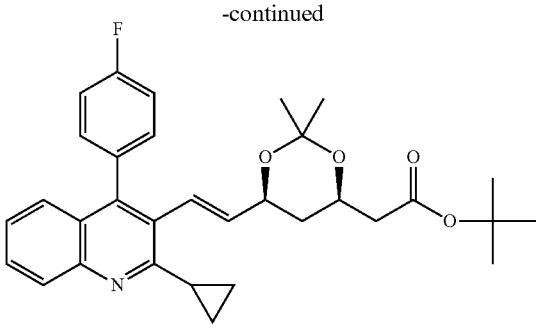


Pitavastatin Lactone Impurity

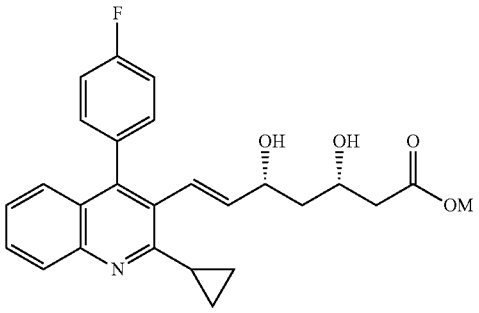


Pitavastatin t-butyl diol ester Impurity

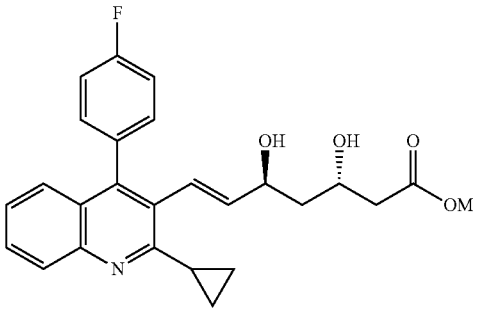
-continued



Pitavastatin Condensed Impurity



Pitavastatin Diastereomer Impurity



Pitavastatin Enantiomeric Impurity

In general, the stability of pitavastatin calcium crystalline form having water content 5% wt/wt at 40° C./75% RH and 25° C./60% RH is shown in Table-1.

TABLE 1

Sr. No.	Conditions of Stability	Initial	1 month 40° C. ± 2° C. RH 75% ± 5%	2 month 40° C. ± 2° C. RH 75% ± 5%	3 month 40° C. ± 2° C. RH 75% ± 5%	3 month 25° C. ± 2° C. RH 60% ± 5%
1	Water by KF (% w/w)	3.0	2.9	4.3	4.2	3.9
2	Related Substances					
	Desflouro	0.05	0.05	0.05	0.05	0.05
	Diastereomer	0.17	0.11	0.11	0.11	0.12
	5-oxo	0.07	0.11	0.15	0.14	0.12
	Lactone	ND	ND	ND	0.09	0.07

TABLE 1-continued

Sr. No.	Conditions of Stability	Initial	1 month 40° C. ± 2° C. RH 75% ± 5%	2 month 40° C. ± 2° C. RH 75% ± 5%	3 month 40° C. ± 2° C. RH 75% ± 5%	3 month 25° C. ± 2° C. RH 60% ± 5%
	Tert-butyl diol ester	ND	ND	ND	ND	ND
	Condensed	ND	ND	ND	ND	ND
	Single Individual	ND	ND	ND	ND	ND
	Total Impurities	0.32	0.28	0.31	0.39	0.36

In another general aspect, there is provided a process for preparation of a stable crystalline form of pitavastatin calcium having water content less than about 5% wt/wt, the process comprising:

a) obtaining a solution of pitavastatin calcium in one or more solvents; and

b) isolating the crystalline pitavastatin calcium optionally, in the presence of one or more anti-oxidants.

In general, the solvent comprises one or more of chlorinated hydrocarbons, alcohols, ketones, aliphatic or cyclic ethers, water, or mixtures thereof. The solvent further comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and water, or mixtures thereof.

According to the embodiments, the anti-oxidants comprises one or more of butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), n-propyl gallant, L-ascorbic acid or α-tocopherol.

Embodiments of the process comprising additional drying of the pitavastatin calcium obtained. The obtained pitavastatin calcium is dried till water content is less than about 5% wt/wt. The further aspect of the process includes packaging the pitavastatin calcium under controlled conditions.

According to still another aspect, the present invention provides a process for the preparation of pitavastatin calcium in stable crystalline form having water content less than about 5% wt/wt, the process comprising:

(a) providing pitavastatin calcium in crystalline form having water content in the range of 8% to 12%;

(b) contacting pitavastatin calcium with humid air in a fluidized bed drier;

(c) maintaining the pitavastatin calcium at a temperature of from about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 hour to about 5 days; and

(d) recovering the pitavastatin calcium in crystalline form having water content less than about 5% wt/wt.

According to one embodiment, the invention present invention provide a process for stabilizing crystalline pitavastatin calcium having water content less than about 5% wt/wt and characteristic peak in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ), the process comprising:

(a) placing crystalline pitavastatin calcium under nitrogen atmosphere in a double polythene bag or non-permeable bag tied with a thread;

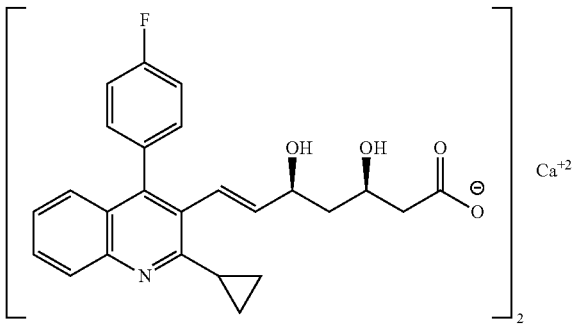
(b) placing the bag of step (a) inside a black color polyethylene bag, optionally containing oxygen busters and sealing it;

(c) placing the bag of step (b) inside a triple laminated bag, optionally containing oxygen busters and sealing it; and

(d) placing the sealed triple laminated bag inside a high density polyethylene (HDPE) container, sealing it and storing in a controlled environment chamber from about 25° C. to about 40° C.

In further general aspect, there is provided a process for the preparation of stable pitavastatin calcium of Formula I

(I)

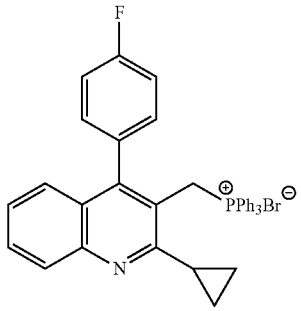


having water content less than about 5% wt/wt and characteristic peak in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ),

the process comprising:

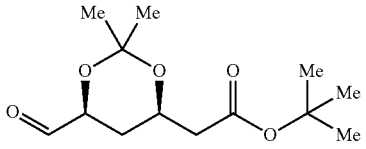
(a) reacting the phosphonium bromide compound of Formula-IV

(IV)



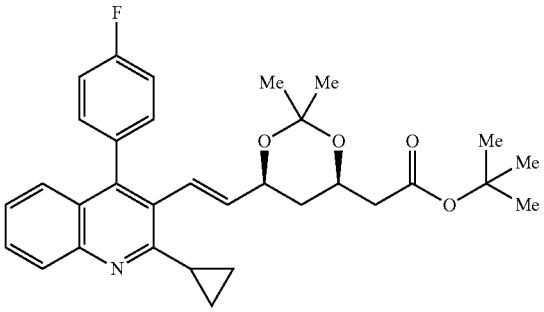
with an aldehyde compound of Formula-III

(III)



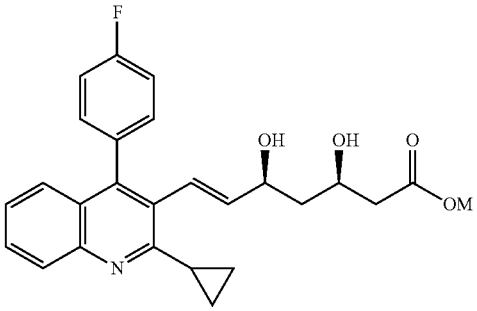
in presence of an alkali or alkaline earth metal bases in one or more of suitable solvent to provide an olefin compound of Formula-II,

(II)



(b) hydrolyzing the olefinic compound of Formula-II by subjecting under the acidic conditions to remove the acetonide and form diol compound, which upon treating with an alkali metal hydroxide base to form the corresponding alkali metal salt of pitavastatin (Ia);

(Ia)



(c) treating the alkali metal salt of pitavastatin (Ia) with a calcium source to obtain pitavastatin calcium (I);

(d) obtaining a solution of pitavastatin calcium in one or more solvents; and

(e) isolating the crystalline pitavastatin calcium optionally, in the presence of one or more anti-oxidants.

In general, the phosphonium bromide compound of Formula-IV and aldehyde compound of Formula-III can be reacted in presence of alkali or alkaline earth metal bases. The alkali or alkaline earth metal bases comprises of one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate and the like, particularly potassium carbonate.

Embodiments includes reaction in suitable solvent comprises one or more of dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methylpyrrolidone or mixtures thereof, particularly dimethylsulfoxide.

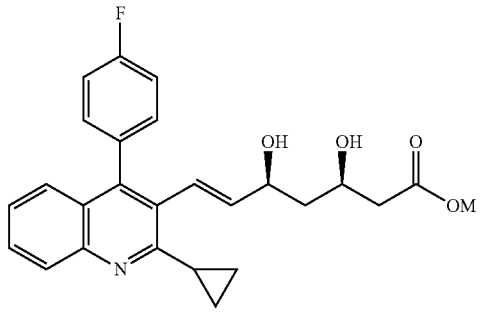
The reaction is at an ambient temperature i.e. at about 15° C. to about 40° C., preferably from about 20° C. to about 35° C. The reaction mixture can be stirred for about 5 to 15 hours till completion of the reaction, preferably for 10 hours. The reaction mixture can be further treated with non-polar solvents like toluene, xylene, methylene dichloride, ethyl acetate for extracting olefin compound of Formula-II, preferably toluene.

The olefin compound of Formula-II can be isolated by removal of toluene followed by addition of isopropanol. After the addition of isopropanol, the reaction mixture can be heated to 40° C. to 80° C., preferably 60° C. to 70° C. and cooling to 15° C. to obtain olefin compound of Formula (II). The compound of Formula (II) can be purified in suitable polar solvent selected from one or more of methanol, ethanol, Isopropanol, acetone, dimethylformamide and the like, particularly methanol.

Further embodiments of the process includes, hydrolysis of olefin compound of Formula (II). The hydrolysis of olefin compound is done by subjecting under the acidic conditions to remove the acetonide and form diol compound. The suitable acid comprises one or more of hydrochloric acid, acetic acid, sulfuric acid, nitric acid, phosphoric acid and the like. In particular, the hydrochloric acid can be used.

The diol compound obtained in-situ is treated with alkali metal hydroxide comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. In particular, sodium hydroxide can be used to obtain corresponding alkali metal salt of pitavastatin (Ia)

(Ia)



herein M is Na^+.

Embodiments of the process include treating alkali metal salt of Formula (Ia) of pitavastatin, preferably pitavastatin sodium with calcium source. The preferred calcium source comprises one or more of calcium chloride, calcium methoxide, calcium acetate and hydrates thereof. In particular, calcium chloride hexahydrate can be used as calcium source.

In general, the solvent in step (d) comprises one or more of chlorinated hydrocarbons, alcohols, ketones, aliphatic or cyclic ethers, water, or mixtures thereof. Particularly, the solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and water, or mixtures thereof.

The suitable anti-oxidant comprises of one or more of butylated hydroxy toluene, butylated hydroxy anisole, n-propyl gallant, L-ascorbic acid or α-tocopherol, preferably, butylated hydroxy anisole.

In general, the pitavastatin calcium prepared by the process as described above, can be dried under vacuum in hot air oven at 60° C. to 65° C. for about 1 to 5 hours to obtain pitavastatin calcium having water content limit in the range of 2.0 to 4.0%. Hence, it is also the scope of the present invention, to dry pitavastatin calcium till constant weight of less than 5% to provide stable pitavastatin calcium.

Embodiments includes drying pitavastatin calcium containing about 8% to 12% water content by Karl Fisher method for about 1 hour to about 5 hours, particularly at least about 1 hour so as obtain less than 5% wt/wt of water content to provide stable pitavastatin calcium.

According to the further embodiments, there is provided a process for the preparation of pitavastatin calcium in crystalline form having water content less than about 5% wt/wt and characteristic peak in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ), the process comprising:

(a) providing a solution comprising pitavastatin calcium (I) in a suitable organic solvent wherein the organic solvent is selected from one or more of chlorinated solvent, alcoholic solvent, ketonic solvent, aliphatic or cyclic ether and mixtures thereof;
(b) adding suitable antisolvent and mixture thereof to the solution; and
(c) recovering the crystalline form of pitavastatin calcium optionally in presence of anti-oxidants;
(d) drying crystalline pitavastatin calcium till water content is less than about 5% wt/wt; and
(b) stabilizing crystalline pitavastatin calcium by packing under controlled condition.

The process for preparation of crystalline pitavastatin calcium includes, addition of anti-solvent to a concentrated solution of pitavastatin calcium in an organic solvent.

Embodiments of the process includes preparing the solution of pitavastatin calcium in suitable organic solvent selected from one or more of chlorinated solvent, alcoholic solvent, ketonic solvent, aliphatic or cyclic ether and mixtures thereof. The preferred solvent can be selected from one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and water or mixtures thereof. In particular, acetone or tetrahydrofuran.

In general, the embodiments of the process include adding suitable antisolvent to the solution of pitavastatin calcium in suitable organic solvent. The suitable anti-solvent can be selected from one or more of hexane, heptane, cyclohexane, toluene, xylene, ethyl acetate and the like. In particular, heptane or cyclohexane.

It is preferable that the anti-solvent and solvent are miscible. The crystalline form can be prepared by further drying and stabilization to obtain stable pitavastatin calcium by removal of solvent from the solution of Pitavastatin Calcium in a suitable solvent.

In another preferred feature, the anti-oxidant is selected from the group consisting of butylated hydroxy toluene, butylated hydroxy anisole, n-propyl gallant, L-ascorbic acid or a-tocopherol. In particular, butylated hydroxy toluene (BHT) or butylated hydroxy anisole (BHA).

According to the further embodiment, there is provided substantially pure pitavastatin calcium in stable crystalline form.

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatin calcium having water content less than about 5% and substantially free from one or more of its corresponding impurities as measured by HPLC.

The impurities as measured by HPLC comprises one or more of desflouro impurity, cis-isomer impurity, pitavastatin 5-oxo impurity, pitavastatin lactone impurity, pitavastatin t-butyl diol ester impurity and pitavastatin condensed impurity when measured by area percentage of HPLC. Further, the aspect also includes impurities like pitavastatin enantiomeric impurity and pitavastatin diastereoisomer impurity.

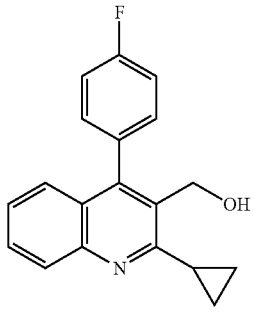
In another aspect, the present invention accordingly provides a pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatin calcium having water content of less than about 5% and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another aspect, the present invention accordingly provides a pharmaceutical composition comprising crystalline pitavastatin calcium having water content of less than 5% substantially free of crystal Form A having a peak of relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

In an aspect of the present application, there is provided crystalline pitavastatin calcium characterized by X-ray powder diffraction peaks at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ) having a particle size distribution wherein the 10^{th} volume percentile particle size (D_{10}) is less than about 20 μm, the 50th volume percentile particle size (D_{50}) is less than about 50 μm, or the 90^{th} volume percentile particle size (D_{90}) is less than about 80 μm, or any combination thereof.

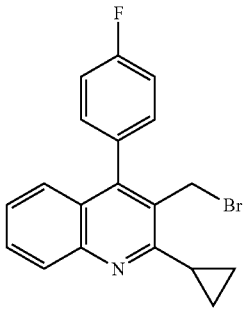
The starting material, phosphonium bromide compound of Formula-IV, can be prepared from alcoholic compound of Formula (VI)

(VI)



The alcoholic compound of Formula (VI) is converted o phosphonium compound of Formula (IV) via formation of 3-(bromomethyl)-2-cyclopropyl-4(4'-flourophenyl)quinoline of Formula (V) by the known process reported in the prior art. WO 95/11898 A1 in its reference example-7 and Example-1 or as per the process disclosed in U.S. Pat. No. 6,627,636 and U.S. Pat. No. 5,763,675.

(V)



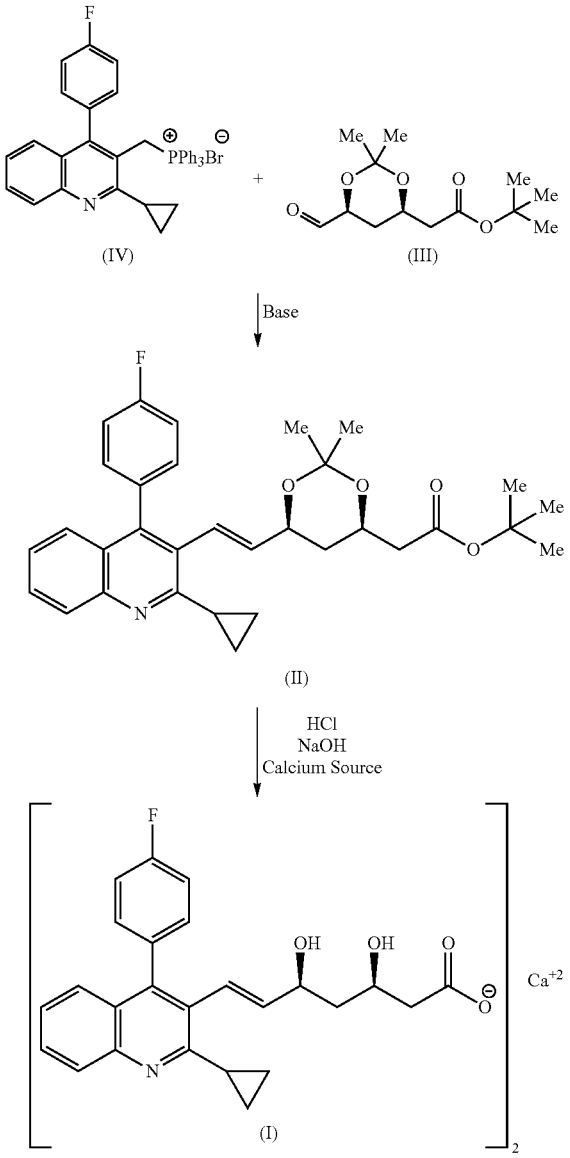
The bromo compound of Formula (V) 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline with wittig reagent like triphenyl phosphine in suitable non-polar sol-

vents like toluene, o-xylene, chlorobenzene etc to obtain phosphonium bromide compound of Formula (IV).

The starting reagent, alcohol compound of Formula (VI) can be prepared from the known process reported in the art like *Tetrahedron Letters, Vol.* 34, No. 51, p.p. 8271-8274 (1993); *Heterocycles, Vol.* 50, No. 1, 1999; *Drugs of Future* 1998 23 (8) or *Tetrahedron Asymmetry* 1993, Vol. 4, pp. 201-204 are reported herein as reference in its entirety.

As set forth in the following schemes, the process of the invention for the preparation of Febuxostat involves the following chemical reactions.

Scheme-2



The crystalline form of pitavastatin calcium can be characterized by PXRD, DSC, and IR as follows:

(a) Characterization by PXRD

The X-ray powder diffraction spectrum was measured under the following experimental conditions:

Instrument: X-Ray Diffractometer, D/Max-2200/PC Make: Rigaku, Japan.

X-Ray: Cu/40 kv/40 mA

Diverging: 1°

Scattering Slit: 1°

Receiving Slit: 0.15 mm

Monochromator RS: 0.8 mm

Counter: Scintillation Counter

Scan Mode: Continuous

Scan Speed: 3.000°/Min

Sampling Width: 0.020

Scan Axes: Two Theta/Theta

Scan Range: 2.000° to 40.000°

Theta Offset: 0.000°

(b) Characterization by Differential Scanning Calorimetry (DSC)

Analytical Method:

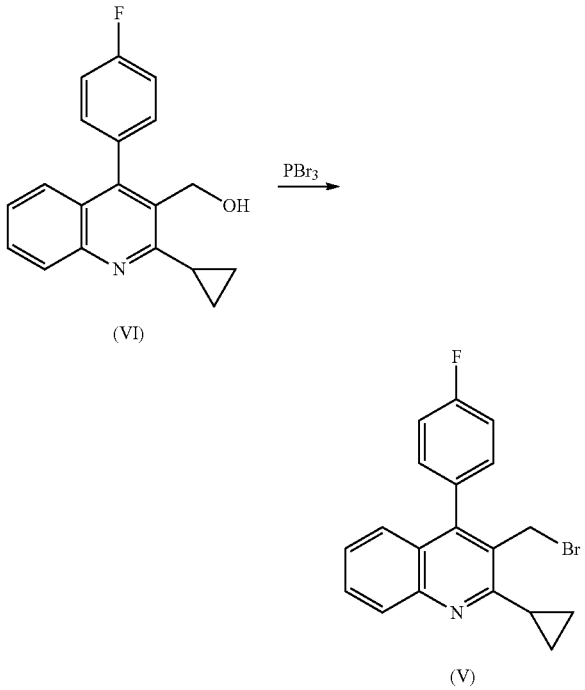
Differential scanning calorimetric analysis was performed using a Perkin Elmer Diamond DSC control unit and a DSC 300° C. differential scanning calorimeter. 2-5 mg samples were placed in crimped aluminum pans and heated from 50° C. to 250° C. in a liquid nitrogen atmosphere at a heating rate of 10° C./minute. Zinc-Indium was used as the standard substance.

(c) The IR spectrum was measured by the KBr method.

The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to; limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications.

Preparation-1:

Preparation of 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline (V)

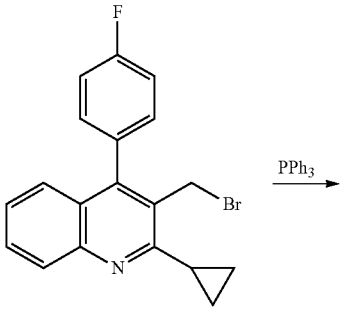


1 Kg of alcohol compound of Formula (VI) and 8 L of methylene dichloride were taken in reactor at 0° C. 0.462 Kg of freshly prepared phosphonium bromide solution in 2 L

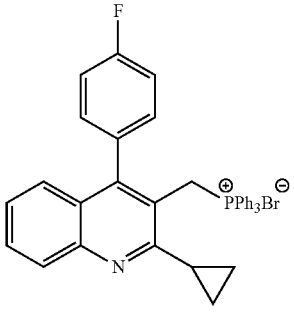
methylene dichloride was added slowly and stirred at 25° C. for 2 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was quenched with 5% sodium bicarbonate solution to adjust the pH from 7-8. The organic layer was separated and washed with 5 L water followed by removal of solvent under vacuum at 45° C. The residue was treated with 2.5 L heptane at 60° C. and cooled to 15° C. The product was filtered at 15° C. and dried under vacuum at 55° C. for 8 hours to obtain 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline.

Preparation-2:

Preparation of Phosphonium Bromide Compound of Formula (IV)



(V)

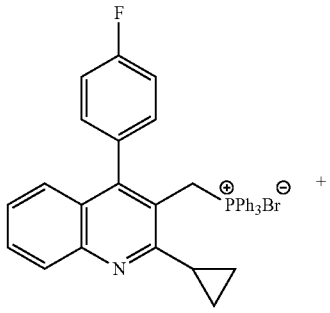


(IV)

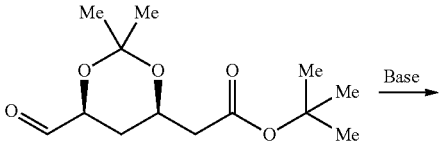
1 Kg of 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline, 10 L of toluene and 300 mL of isopropanol were taken in reactor and heated at 50° C. 0.874 Kg of triphenyl phosphine solution in 2 L toluene was added slowly and stirred for 3 hours. The reaction mixture was cooled to 25° C. and stirred for 1 hour. The product was filtered and washed with toluene. The product was dried in tray dryer at 55° C. for 8 hours to obtain phosphonium bromide compound of Formula (IV).

Example-1

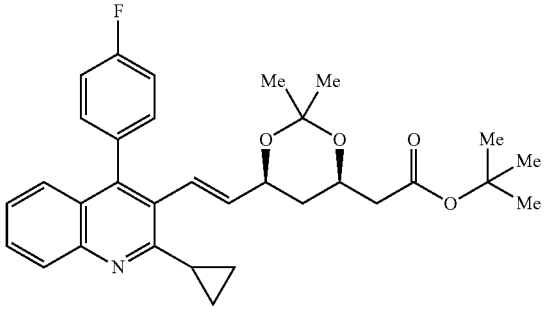
Preparation of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of Formula II



(IV)



(III)



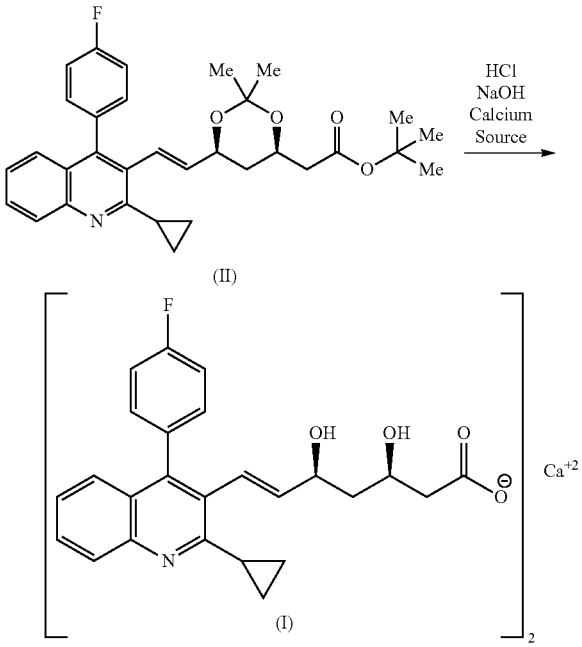
(II)

To a solution of 0.751 Kg of tert-butyl-2-((4R,6S)-6-formul-2,2-dimethyl-1,3-dioxan-4-yl)acetate (III) in 7 L of dimethylsulphoxide, was added 1 Kg of phosphonium bromide compound of Formula (IV) and 0.67 Kg of potassium carbonate. The reaction mixture was stirred at 25° C. for 10 hours under nitrogen atmosphere. The reaction mixture was quenched with water and extracted with toluene. The organic

layer was concentrated and the compound of Formula (II) was isolated using isopropanol. The product thus obtained was recrystallized in methanol.

Example-2

Preparation of Pitavastatin Calcium of Formula (I)



To a solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of Formula II in 1 L methanol, was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution. The reaction mixture was stirred for 4 hours at 25° C. and quenched in water (preboiled). The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH to about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer was treated with 100 g of calcium chloride hexahydrate and stirred for 30 min at 25° C. The solution was cooled to 15° C., filtered and washed with water. The product was dried in hot air oven for 12 hours to obtain 82 g of crystalline pitavastatin calcium having water content from about 8% to 12.0%. The wet-cake was dried under vacuum at 60 to 65° C. for 1-5 hours to get water content from about 2.0 to 4.0% w/w.

Example 3

Preparation of Crystalline Pitavastatin Calcium

10 g of crystalline pitavastatin calcium was dissolved in a mixture of 25 ml THF and 25 ml water. To this stirred solution, was slowly added 10 ml n-heptane at room temperature, and stirred for an additional 16 hours. The resulting suspension was filtered and dried in air. The obtained solid was crystalline form having water content more than 8%. The product was dried in hot air oven for about 12 hours under vacuum to obtain 8.2 g of crystalline pitavastatin calcium having water content of 3.0% having the X-ray diffraction pattern depicted in FIG. **1**.

Example 4

Preparation of Crystalline Pitavastatin Calcium

10 g of pitavastatin calcium having water content 8% to 12% of example-2 was dried in a Fluid Bed Dryer at 45° C. for 2 days to obtain crystalline pitavastatin calcium having water content less than 3.5% wt/wt. An X-ray diffraction study on the product showed it to be crystalline (FIG. **1**.)

Example 5

Preparation of Crystalline Pitavastatin Calcium

10 g of pitavastatin calcium having water content 8% to 12% was dried in a vacuum tray dryer at about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of 24 hours to obtain crystalline pitavastatin calcium having water content less than 5% wt/wt. An X-ray diffraction study on the product showed it to be crystalline (FIG. **1**.)

Example 6

Packing of Crystalline Pitavastatin Calcium

The crystalline pitavastatin calcium obtained in example-2 having water content of about 3.1% was placed under nitrogen atmosphere in a double polythene bag or non-permeable bag tied with a thread, placing the above bag inside a black color polyethylene bag, optionally containing oxygen busters and sealing it, placing above the black color polyethylene inside a triple laminated bag optionally containing oxygen busters and sealing it, and placing the sealed triple laminated bag inside a closed high density polyethylene (HDPE) container, sealing it and storing in a controlled environment chamber from about 25° C. to about 40° C.

ADVANTAGES OF THE INVENTION

1. The present invention provides crystalline pitavastatin calcium having water content less than about 5% wt/wt.
2. The present invention provides storage stable crystalline pitavastatin calcium having water content less than about 5% wt/wt.
3. The present invention provides crystalline pitavastatin calcium having at least one or more of following impurities less than 0.15% by area percentage of HPLC. pitavastatin desflouro; pitavastatin diastereomer; pitavastatin 5-oxo; pitavastatin lactone; pitavastatin tert butyl diol ester; pitavastatin condensed; pitavastatin enantiomer or any other unknown single individual impurity.
4. The present invention also provides crystalline pitavastatin calcium substantially free from crystal Form A having a peak of relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.
5. The present invention provides stable pitavastatin calcium containing after exposure to a relative humidity of 75% at 40° for a period of at least three months.
6. The present invention provides stable pitavastatin calcium containing after exposure to a relative humidity of 60% at 25° for a period of at least three months.
7. The process provided is eco-friendly, economically viable and easily scalable on large scale production.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. Storage stable pitavastatin calcium having a water content less than about 5% wt/wt and having characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2°.

2. The stable pitavastatin calcium as claimed in claim **1**, wherein the pitavastatin calcium has the X-ray powder diffraction pattern as shown in FIG. **1**.

3. The stable pitavastatin calcium as claimed in claim **1**, wherein the pitavastatin calcium is substantially free of crystal Form-A, wherein Crystal Form-A is characterized by having an X-ray powder diffraction peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

4. The stable pitavastatin calcium as claimed in claim **1**, wherein the pitavastatin calcium is substantially free of crystal Form-A of pitavastatin calcium characterized by the absence of an X-ray powder diffraction peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

5. The stable pitavastatin calcium as claimed in claim **1**, wherein the pitavastatin calcium is substantially free of crystal Form-A of pitavastatin calcium characterized by the absence of an X-ray powder diffraction peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16° after storage for 3 months at 40° C. and a relative humidity of 75%.

6. The stable pitavastatin calcium as claimed in claim **1**, wherein the pitavastatin calcium is substantially free of crystal Form-A of pitavastatin calcium characterized by the absence of an X-ray powder diffraction peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16° after storage for 3 months at 25° C. and a relative humidity of 60%.

7. Stable crystalline pitavastatin calcium having characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2°, which is substantially free of crystal Form-A of pitavastatin calcium, in which the absence of Form A pitavastatin calcium is characterized by the absence of and does not show a X-ray powder diffraction peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

8. The stable pitavastatin calcium as claimed in claim **1**, which is substantially pure.

9. A process for the preparation of a stable crystalline form of pitavastatin calcium according to claim **1**, wherein the crystalline pitavastatin calcium has a water content of less than about 5% wt/wt and characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2°, the process comprising:

a) obtaining a solution of pitavastatin calcium in one or more solvents; and

b) isolating the crystalline pitavastatin calcium optionally, in the presence of one or more anti-oxidants.

10. The process as claimed in claim **9**, wherein the solvent comprises one or more of chlorinated hydrocarbons, alcohols, ketones, aliphatic or cyclic ethers, water, or mixtures thereof.

11. The process as claimed in claim **9**, wherein the solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and water, or mixtures thereof.

12. The process as claimed in claim **9**, wherein the anti-oxidant comprises one or more of butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), n-propyl gallant, L-ascorbic acid or a-tocopherol.

13. The process as claimed in claim **9**, further comprising additional drying of the pitavastatin calcium obtained.

14. The process as claimed in claim **13**, wherein the pitavastatin calcium is dried till water content is less than about 5% wt/wt.

15. The process as claimed in claim **13**, further comprising packaging the pitavastatin calcium under controlled conditions.

16. A process for the preparation of pitavastatin calcium according to claim **1**, wherein the crystalline pitavastatin calcium has a water content of less than about 5% wt/wt and characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2°, the process comprising:

(a) providing the pitavastatin calcium in crystalline form having a water content in the range of 8% to 12%;

(b) contacting the pitavastatin calcium with humid air in a fluidized bed drier;

(c) maintaining the pitavastatin calcium at a temperature of from about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 hour to about 5 days; and

(d) recovering the pitavastatin calcium in crystalline form having a water content less than about 5% wt/wt.

17. A process for stabilizing crystalline pitavastatin calcium according to claim **1**, wherein the crystalline pitavastatin calcium has a water content of less than about 5% wt/wt and characteristic peaks in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2° (2θ), the process comprising:

(a) placing crystalline pitavastatin calcium under nitrogen atmosphere in a double polythene bag or non-permeable bag tied with a thread;

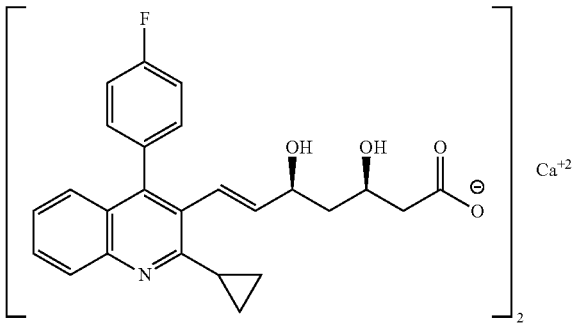
(b) placing the bag of step (a) inside a black color polyethylene bag, optionally containing oxygen busters and sealing it;

(c) placing the bag of step (b) inside a triple laminated bag, optionally containing oxygen busters and sealing it; and

(d) placing the sealed triple laminated bag inside a high density polyethylene (HDPE) container, sealing it and storing in a controlled environment chamber from about 25° C. to about 40° C.

18. A process for the preparation of stable pitavastatin calcium of Formula I according to claim **1**,

(I)

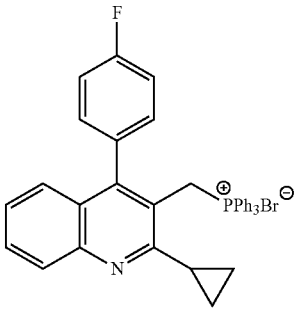


wherein the crystalline pitavastatin calcium has a water content of less than about 5% wt/wt and characteristic peaks in X-ray powder diffraction at about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2° (2θ),

the process comprising:

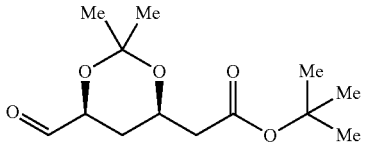
(a) reacting the phosphonium bromide compound of Formula-IV

(IV)



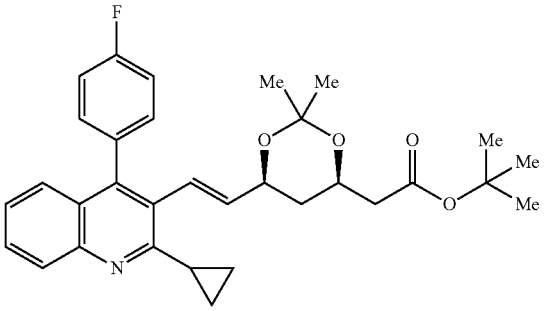
with an aldehyde compound of Formula-III

(III)



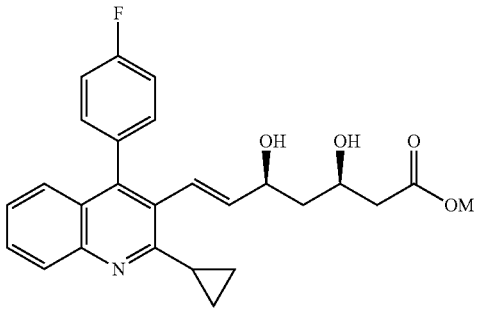
in the presence of an alkali or alkaline earth metal bases in one or more of suitable solvents to provide an olefin compound of Formula-II;

(II)



(b) hydrolyzing the olefinic compound of Formula-II by subjecting under the acidic conditions to remove the acetonide and form diol compound, which upon treating with an alkali metal hydroxide base to form the corresponding alkali metal salt of pitavastatin (Ia);

(Ia)



(c) treating the alkali metal salt of pitavastatin (Ia) with a calcium source to obtain pitavastatin calcium (I);

(d) obtaining a solution of pitavastatin calcium in one or more solvents; and

(e) isolating the crystalline pitavastatin calcium optionally, in the presence of one or more anti-oxidants.

19. The process as claimed in claim **18**, wherein the alkali or alkaline earth metal bases comprise of one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, and cesium carbonate.

20. The process as claimed in claim **18**, wherein the suitable solvent in step (a) comprises one or more of dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methyl-pyrrolidone, or mixtures thereof.

21. The process as claimed in claim **18**, wherein the suitable acid comprises one or more of hydrochloric acid, acetic acid, sulfuric acid, nitric acid, and phosphoric acid.

22. The process as claimed in claim **18**, wherein the alkali metal hydroxide comprises one or more of sodium hydroxide, potassium hydroxide, and lithium hydroxide.

23. The process as claimed in claim **18**, wherein the suitable calcium source comprises one or more of calcium chloride, calcium methoxide, calcium acetate and hydrates thereof.

24. The process as claimed in claim **18**, wherein the solvent in step (d) comprises one or more of chlorinated hydrocarbons, alcohols, ketones, aliphatic or cyclic ethers, water, or mixtures thereof.

25. The process as claimed in claim **24**, wherein the solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and water, or mixtures thereof.

26. The process as claimed in claim **25**, wherein the anti-oxidant comprises one or more of butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), n-propyl gallant, L-ascorbic acid or a-tocopherol.

27. A pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatin calcium having characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2° and a water content of less than about 5%, and one or more pharmaceutically acceptable carriers, excipients or diluents.

28. A pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatin calcium having characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2° and a water content of less than about 5% and

substantially free from one or more of its corresponding impurities as measured by HPLC.

29. A pharmaceutical composition comprising crystalline pitavastatin calcium having characteristic X-ray powder diffraction peaks at 2-theta values of about 6.7°, 9.0°, 11.1°, 19.6°, and 21.0°±0.2°, a water content of less than 5%, and being substantially free of crystal Form A of pitavastatin calcium characterized by having a peak of relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

30. Crystalline pitavastatin calcium characterized by X-ray powder diffraction peaks at about 6.7°, 9.0°, 11.1°, 19.6°, 21.0°±0.2° (2θ) having a particle size distribution wherein the 10^{th} volume percentile particle size (D_{10}) is less than about 20 μm, the 50^{th} volume percentile particle size (D_{50}) is less than about 50 μm, or the 90^{th} volume percentile particle size (D_{90}) is less than about 80 μm, or any combination thereof.

31. The stable pitavastatin calcium as claimed in claim **8**, wherein the substantially pure pitavastatin calcium contains less than about 0.15% (wt/wt) of any single impurity.

32. The stable pitavastatin calcium as claimed in claim **8**, wherein the substantially pure pitavastatin calcium contains less than about 0.3% (wt/wt) of any pitavastatin diastereomeric impurity and pitavastatin enantiomeric impurity.

* * * * *

EXHIBIT F

US009139527B2

(12) **United States Patent**
Dwivedi et al.

(10) **Patent No.: US 9,139,527 B2**
(45) **Date of Patent: Sep. 22, 2015**

(54) **METHOD OF PREPARATION OF PITAVASTATIN AND PHARMACEUTICAL ACCEPTABLE SALTS THEREOF**

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(72) Inventors: **Shriprakash Dhar Dwivedi**, Gujarat (IN); **Dhimant Jasubhai Patel**, Gujarat (IN); **Alpesh Pravinchandra Shah**, Gujarat (IN); **Brij Khera**, Princeton, NJ (US)

(73) Assignee: **Cadila Healthcare Limited**, Ahmedabad (IN)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/479,575**

(22) Filed: **Sep. 8, 2014**

(65) **Prior Publication Data**

US 2015/0152061 A1 Jun. 4, 2015

Related U.S. Application Data

(62) Division of application No. 13/665,932, filed on Nov. 1, 2012, now Pat. No. 8,829,186, which is a division of application No. 13/009,492, filed on Jan. 19, 2011, now abandoned.

(30) **Foreign Application Priority Data**

Jan. 20, 2010 (IN) 159/MUM/2010

(51) **Int. Cl.**
C07D 215/14 (2006.01)

(52) **U.S. Cl.**
CPC ***C07D 215/14*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2012/0016129 A1* 1/2012 Satyanarayana Reddy et al. 546/173

OTHER PUBLICATIONS

Acemoglu et al., A New and Efficient Synthesis of the HMG-CoA Reductase Inhibitor Pitavastatin, 90(6) Helvetica Chimica Acta 1069-1081 (2007).*

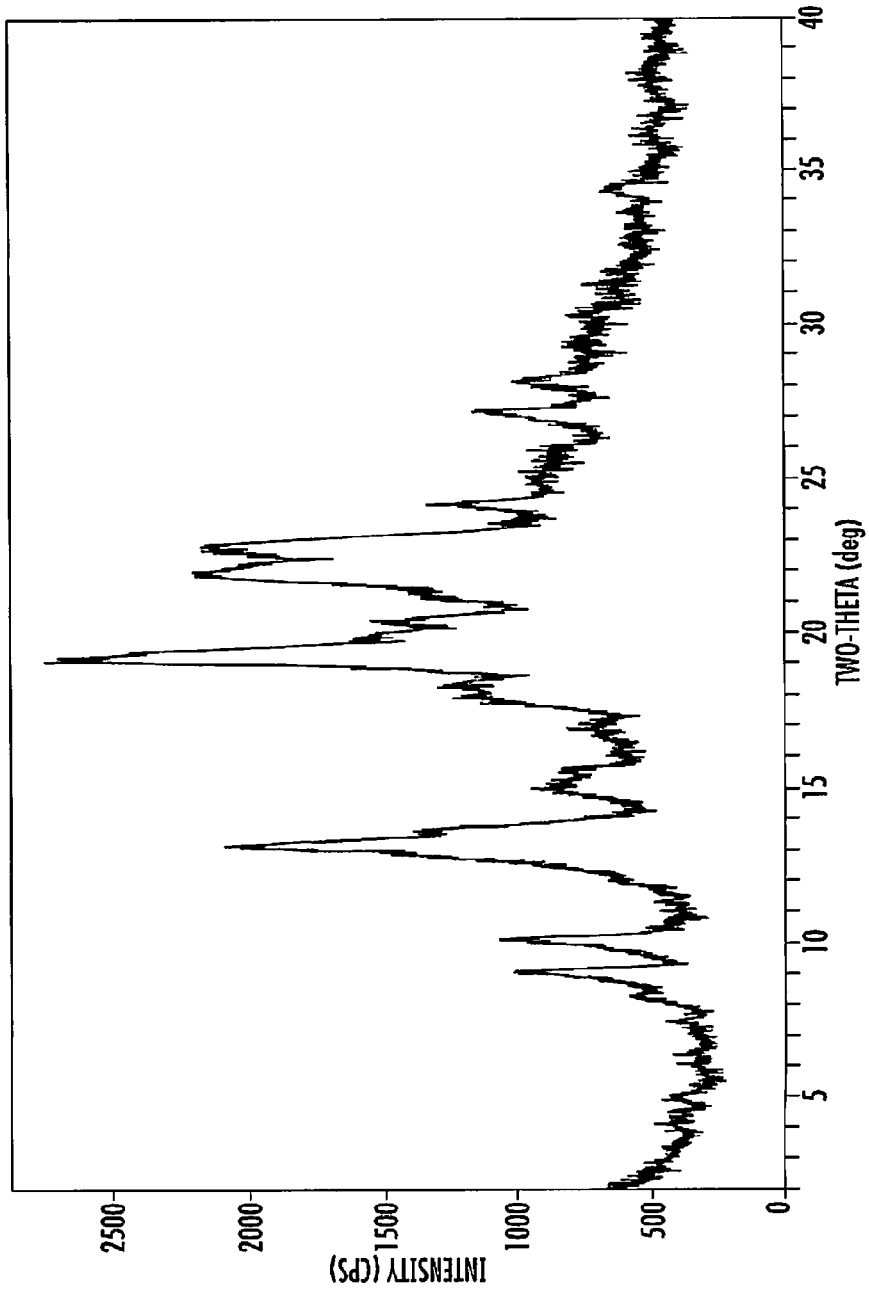
* cited by examiner

Primary Examiner — Timothy R Rozof
(74) *Attorney, Agent, or Firm* — Brij Khera; William D. Hare; McNeely, Hare & War, LLP

(57) **ABSTRACT**

The present invention discloses a compound, which is alkali or alkaline earth metal salts of pitavastatin, wherein the alkali or earth metal comprise one or more of magnesium, zinc, potassium, strontium and barium.

15 Claims, 4 Drawing Sheets


INTENSITY (CPS)
2500
2000
1500
1000
500
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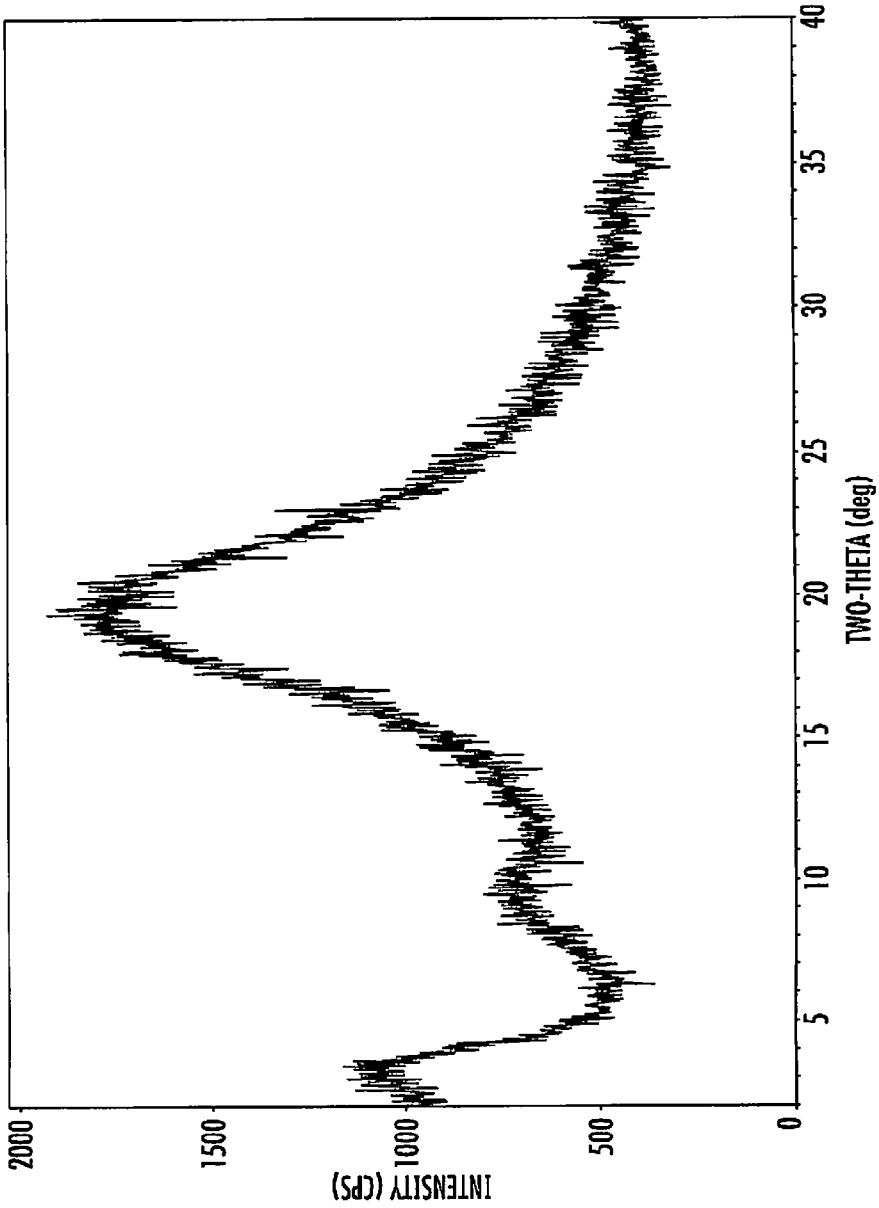
5
10
15
20
25
30
35
40
TWO-THETA (deg)

FIG. 1


INTENSITY (CPS)
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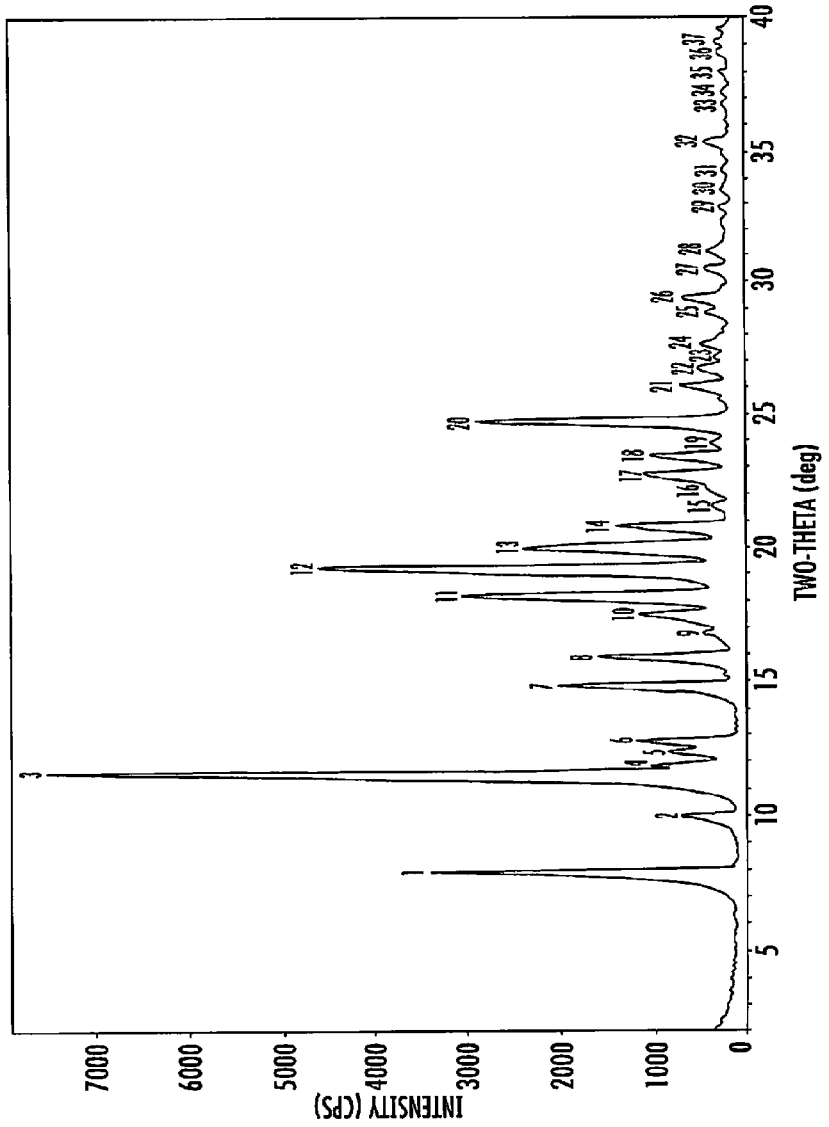
TWO-THETA (deg)

FIG. 2


INTENSITY (CPS)
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1000
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4000
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6000
7000
TWO-THETA (deg)
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10
15
20
25
30
35
40

FIG. 3

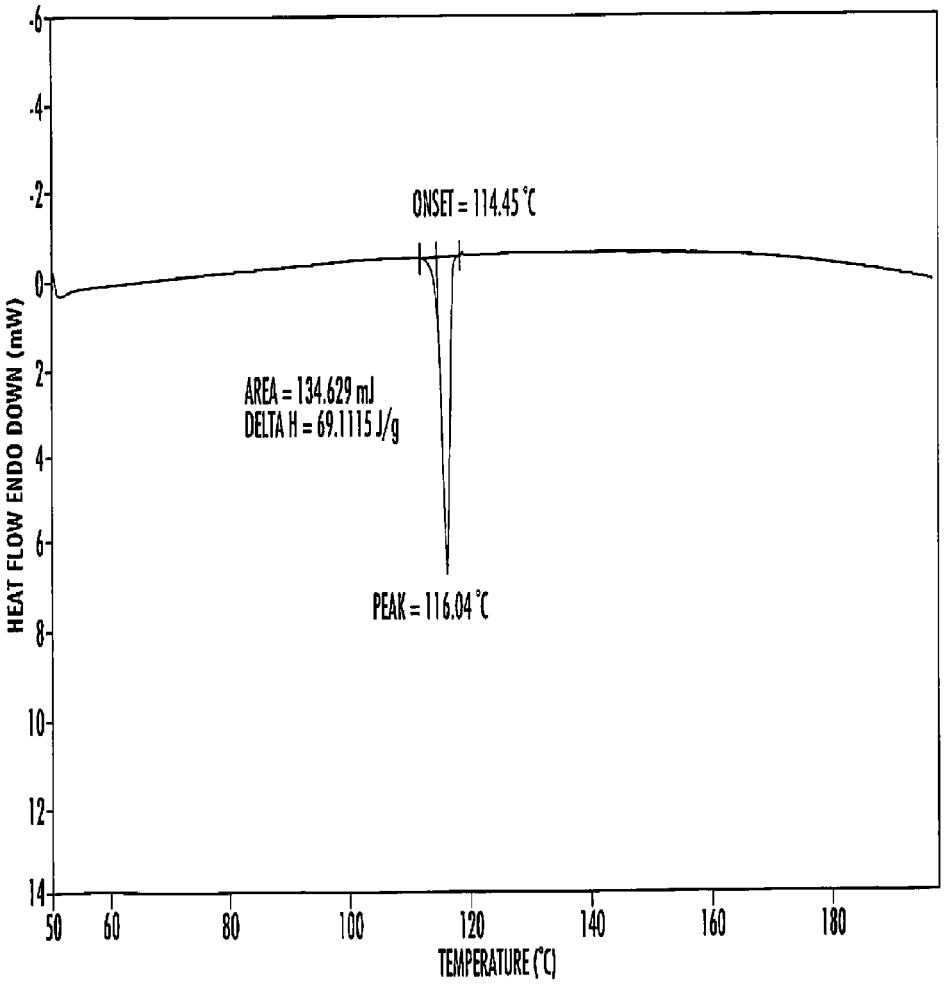

ONSET = 114.45 °C
AREA = 134.629 mJ
DELTA H = 69.1115 J/g
PEAK = 116.04 °C
HEAT FLOW ENDO DOWN (mW)
TEMPERATURE (°C)
-6
-4
-2
0
2
4
6
8
10
12
14
50
60
80
100
120
140
160
180

FIG. 4

METHOD OF PREPARATION OF PITAVASTATIN AND PHARMACEUTICAL ACCEPTABLE SALTS THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 13/665,932, filed on Nov. 1, 2012, which is a divisional application of U.S. patent application Ser. No. 13/009,492, filed on Jan. 19, 2011, which claims priority to Indian Application No. 159/MUM/2010 filed on Jan. 20, 2010.

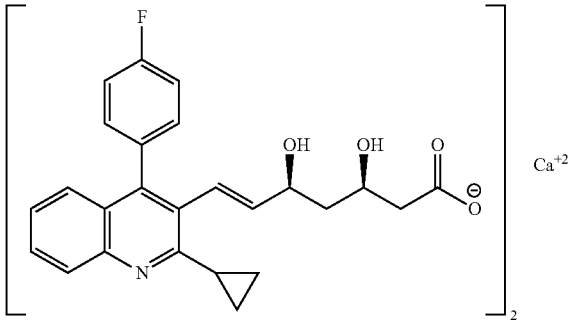
FIELD OF THE INVENTION

The present invention relates to processes for the preparation of pitavastatin and pharmaceutically acceptable salts thereof. In particular, the present invention provides processes for the preparation of pitavastatinalkali or alkaline earth metal salts in crystalline and amorphous forms.

BACKGROUND OF THE INVENTION

Pitavastatin calcium is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-flourophenyOquinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid calcium salt having the formula IA is known in the literature.

(IA)



Pitavastatin is a synthetic lipid-lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase (HMG-CoA Reductase inhibitor). This enzyme catalyzes the conversions of HMG-CoA to mevalonate, inhibitors are commonly referred to as "statins". Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. Pitavastatin is used in the treatment of hyperchloesterolemia and mixed dyslipidemia.

Pitavastatin calcium has recently been developed as a new chemically synthesized and powerful statin by Kowa Company Ltd, Japan. On the basis of reported data, the potency of Pitavastatin is dose-dependent and appears to be equivalent to that of Atorvastatin. This new statin is safe and well tolerated in the treatment of patients with hypercholesterolaemia. Significant interactions with a number of other commonly used drugs can be considered to be extremely low.

Processes for the preparation of Pitavastatin are described in EP-A-0304063 and EP-A-1099694 and in the publications by N. Miyachi et al. in Tetrahedron Letters (1993) vol. 34, pages 8267-8270 and by K. Takahashi et al. in Bull. Chem.

Soc. Japan (1995) Vol. 68, 2649-2656. These publications describe the synthesis of Pitavastatin in great detail but do not describe the hemi-calcium salt of Pitavastatin. The publications by LA. Sorbera et al. in Drugs of the Future (1998) vol. 23, pages 847-859 and by M. Suzuki at al. in Bioorganic & Medicinal Chemistry Letters (1999) vol. 9, pages 2977-2982 describe Pitavastatin calcium, however, a precise procedure for its preparation is not given. A full synthetic procedure for the preparation of Pitavastatin calcium is described in EP-A-0520406. In the process described in this patent Pitavastatin calcium is obtained by precipitation from an aqueous solution as a white crystalline material with a melting point of 190-192° C.

US20090182008 A1 discloses polymorphic form A, B, C, D, E, and F, and the amorphous form of Pitavastatin Calcium salt (2:1). In particular, crystalline Form A having water content from about 5% to about 15% and process for its preparation are disclosed.

US20090176987 A1 also discloses polymorphic form crystal form A of Pitavastatin Calcium which contains from 5 to 15% of water and which shows, in its X-ray powder diffraction as measured by using CuKα radiation, a peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

WO2007/132482 A1 discloses a novel process for the preparation of Pitavastatin Calcium by condensing bromide salt of formula-3 with aldehyde compound of formula-4 to obtain olefinic compound of formula-5 and converting olefinic compound to Pitavastatin Calcium via organic amine salt for purification.

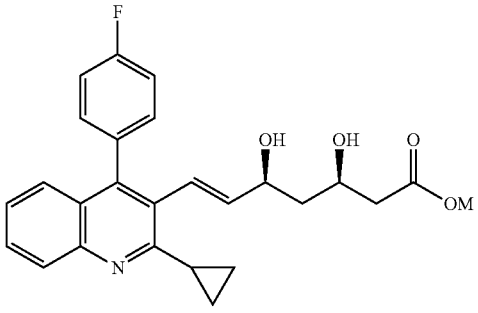
There are no reports available in the prior art for the preparation of Pitavastatin Magnesium. Thus, the inventors of the present inventions provide a novel pharmaceutically acceptable salt of Pitavastatin, preferably magnesium salt.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided alkali or alkaline earth salt of quinoline derivatives such as pitavastatin, a HMG-CoA inhibitors, more specially, the present invention provides a novel process for the preparation of pitavastatinmagnesium it is crystalline and amorphous form.

In one embodiment, there is provided a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salts. In particular, pitavastatinalkali or alkaline earth metalcomprises one or more of magnesium, zinc, potassium, strontium, barium and the like. Pitavastatin, which is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-flourophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid and its pharmaceutically acceptable salts having the general formula I

(I)

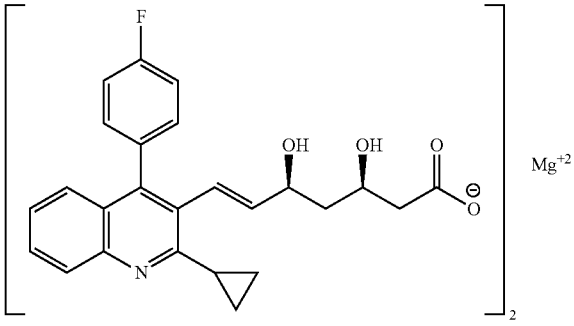


wherein, M is K^+, Mg^{+2}, Sr^{+2}, Zn^{+2}, Ba^{+2}.

In one preferred embodiment, there is provided a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salts, particularly pitavastatinmagnesium which is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-flourophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid Magnesium salt having the formula IB.

In second embodiment, there is provided a novel salt, pitavastatinmagnesium of Formula (IB)

(IB)



In yet another embodiment, there is provided pitavastatinmagnesium it its crystalline form having X-ray powder diffraction peaks at 10.1, 13.2, 19.3 and 27.2±0.2 (20).

In further embodiment, there is provided a process for the preparation of pitavastatinmagnesium of formula (1B), the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-II;

(b) hydrolyzing the compound of Formula-II under the acidic conditions to remove the acetonide protection to form a diol compound;

(c) treating the diol compound of step (b) in-situ with an alkali metal hydroxide to form the corresponding alkali metal salt of pitavastatin (I);

(d) treating alkali metal salt of pitavastatin with a magnesium source to obtain pitavastatinmagnesium; and

(e) isolating the pitavastatinmagnesium.

According to the embodiments, the process for the preparation of pitavastatinmagnesium according to the present inventions provides crystalline form of pitavastatinmagnesium having water content in the range of from about 7% to about 12% wt/wt.

According to another embodiment, the compound (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester of formula (II) in crystalline form.

According to another embodiment, there is provided an improved process for the purification of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester of formula (II) to obtain in crystalline form.

According to the further embodiments, there is provided a process for the preparation of pitavastatinmagnesium in amorphous form, the process comprising:

(a) providing a solution comprising pitavastatinmagnesium in a suitable organic solvent wherein the organic solvent is one or more of a chlorinated solvent, alcoholic solvent, ketonic solvent, aliphatic or cyclic ether and mixtures thereof;

(b) adding suitable antisolvent to the solution; and

(c) recovering the amorphous form of the pitavastatinmagnesium.

According to the further embodiments, there is provided a process for the preparation of an amorphous form of the pitavastatinmagnesium having water content less than about 2% wt/wt, the process comprising:

(a) providing pitavastatinmagnesium in crystalline form having water content in the range of about 8% to about 12% wt/wt;

(b) contacting the pitavastatinmagnesium with humid air in a fluidized bed drier, or maintaining the pitavastatinmagnesium at a temperature of from about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 to 5 days; and

(c) recovering the pitavastatinmagnesium in the amorphous form having water content less than about 2% wt/wt.

According to the further embodiment, there is provided substantially pure pitavastatinmagnesium in stable crystalline form.

DETAILED DESCRIPTION OF DRAWINGS

FIG. **1**: X-ray diffraction pattern of crystalline pitavastatinmagnesium having about 8% to about 12% water content prepared as per the process of Example-2

FIG. **2**: X-ray diffraction pattern of amorphous pitavastatin magnesium prepared as per the process of Example-3

FIG. **3**: X-ray diffraction pattern of crystalline (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)-quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound (II).

FIG. **4**. DSC thermogram of crystalline (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)-quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound (II) having endothermic peak at about 116.04° C.

The details of one or more embodiments of the inventions are set forth in the description below.

Other features, objects and advantages of the inventions will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The prior art discloses the use of organic amine salts of Pitavastatin for obtaining better purity. The present inventors have found that pitavastatinalkali or alkaline earth metal salt prepared by using the process provided herein provides better yield and purity and avoids the use of amine salt formation. This significantly improves the process economics and commercial viability.

As used here in the term "isolation" may include filtration, filtration under vacuum, centrifugation, and decantation. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

Optionally, the solution, prior to any solids formation, can be filtered to remove any undissolved solids, solid impurities and the like prior to removal of the solvent. Any filtration system and filtration techniques known in the art can be used.

The term "Suitable organic solvent" means a single or a combination of two or more solvents.

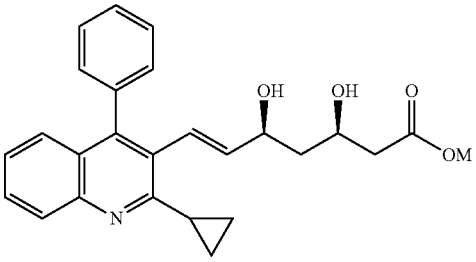
The term "Substantially pure" means pitavastatinalkali or alkaline earth metal prepared by the process of the present invention is substantially free from any single individual

impurities like desflouro impurity, cis-isomer impurity, Pitavastatin 5-oxo impurity, pitavastatinlactone impurity, pitavastatin t-butyl diol ester impurity, and pitavastatincondensed impurity.

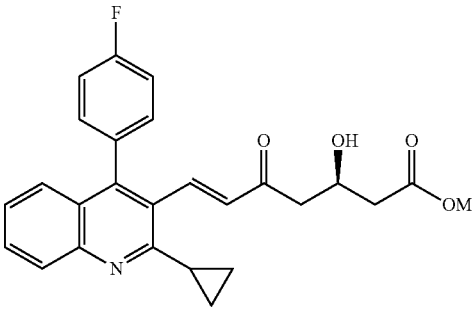
Further the term "substantially pure" means pitavastatinalkali or alkaline earth having purity greater than 99%. In particular, it may be greater than 99.5% by area percentage of HPLC. In particular, containing less than about 0.1% of single individual impurity as herein described above and total impurities not more than 1.0% by area percentage of HPLC.

Particularly, pitavastatindiastereomeric impurity and pitavastatinenantiomeric impurity are present less than about 0.3% by area percentage of HPLC.

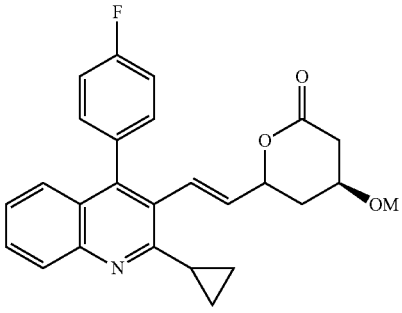
The above impurities are present in the preparation of pitavastatinalkali or alkaline earth metal salts includes the following which were determined from an HPLC analysis of different batches of pitavastatinalkali or alkaline earth metal salts produced by the method described in the specification herein after:



Des-Flouro Pitavastatin

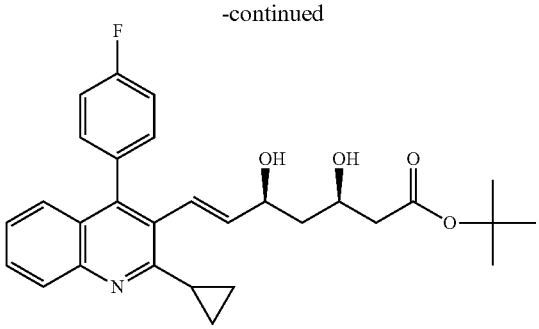


Pitavastatin 5-oxo Impurity

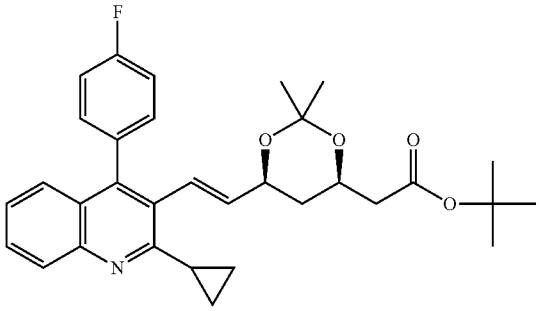


Pitavastatin Lactone Impurity

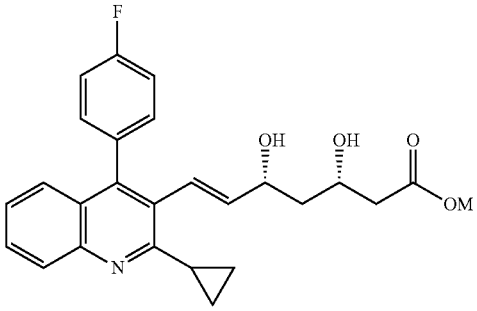
-continued



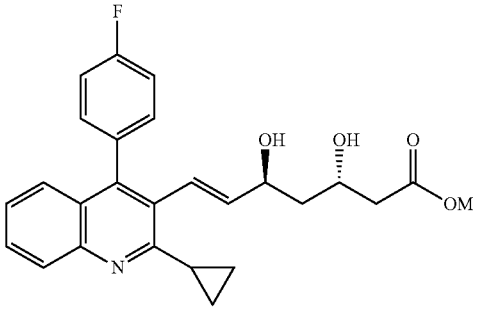
Pitavastatin t-butyl diol ester Impurity



Pitavastatin Condensed Impurity



Pitavastatin Diastereomer Impurity

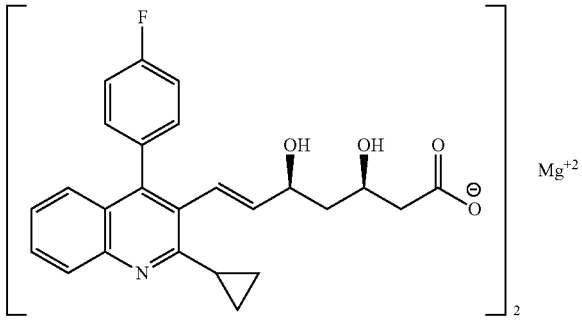


Pitavastatin Enantiomeric Impurity

In first embodiment, there is provided alkali or alkaline earth metal salts of pitavastatin, wherein the alkali or alkaline earth metal comprises one or more of magnesium, zinc, potassium, strontium, barium and the like. In particular, it may comprises one or more of magnesium, zinc and potassium.

In second embodiment of the present invention, there is provided a novel salt pitavastatin magnesium of Formula (IB)

(IB)



In particular, the pitavastatin magnesium may be a hydrate having water content in the range of from about 7% to about 12% wt/wt. In particular, the water content may be about 9% to about 12% wt/wt. More particularly, the water content may be about 10% to about 12% wt/wt as measured by the known techniques in the art like Karl-Fisher method.

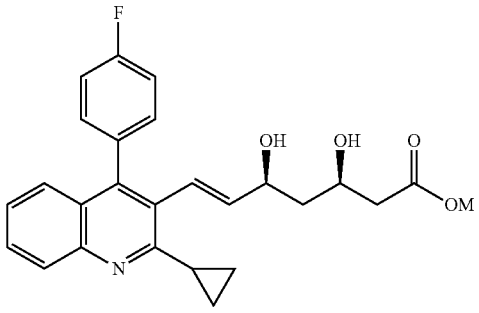
In yet another embodiment, there is provided pitavastatin magnesium in crystalline form having x-ray powder diffraction peaks at 10.1, 13.2, 19.3 and 27.2±0.2 (2θ). In particular, the pitavastatin magnesium crystalline form is having an x-ray powder diffraction pattern as shown in FIG. **1**. Further embodiment includes pitavastatin magnesium having optical rotation of about +22.0 to +22.5 in 1% DMSO at 20±0.5° C.

In yet another embodiment, there is provided an amorphous form of the pitavastatin magnesium having x-ray powder diffraction peaks as shown in FIG. **2**. According to further embodiment, the amorphous form of pitavastatin magnesium is having the water content less than about 5% wt/wt. In particular, it may have the water content less than about 2% wt/wt.

In a third embodiment, there is provided a process for the preparation of pitavastatin and its pharmaceutically acceptable salts, in particular pitavastatin alkali or alkaline earth metal comprises one or more of magnesium, potassium, zinc and the like.

The pitavastatinalkali metal salts is chemically known as (3R,5S)-7-[2-cyclopropyl-4-(4-flourophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid salt having the general Formula (I)

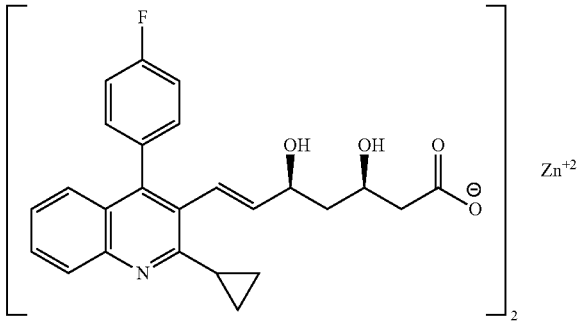
(I)



wherein, M is Na^+, K^+, Li^+.

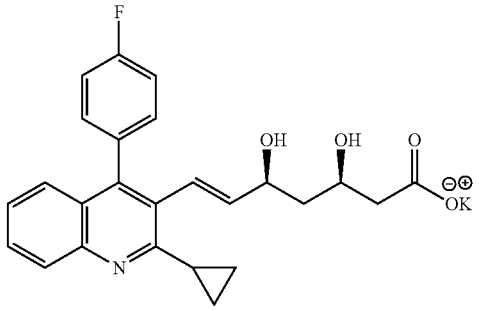
In a further embodiment of the present invention, there is provided a pitavastatinzinc of Formula (IC)

(IC)



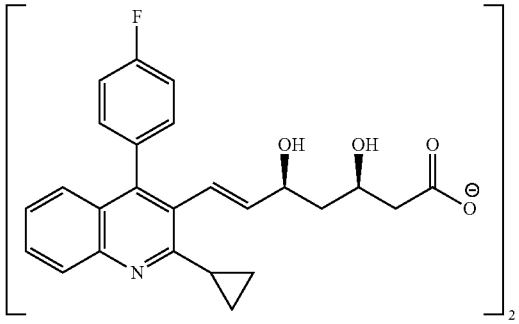
In yet another aspect of the present invention, there is provided a pitavastatinpotassium of formula (ID)

(ID)



According to a further embodiment, there is provided a process for the preparation of pitavastatinmagnesium of formula (IB),

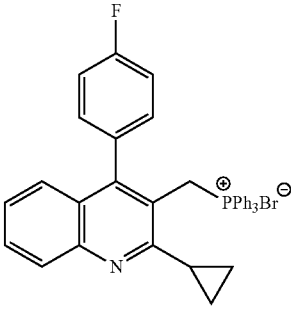
(IB)



the process comprising:

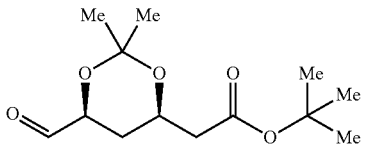
(a) reacting phosphonium bromide compound of Formula-IV

(IV)



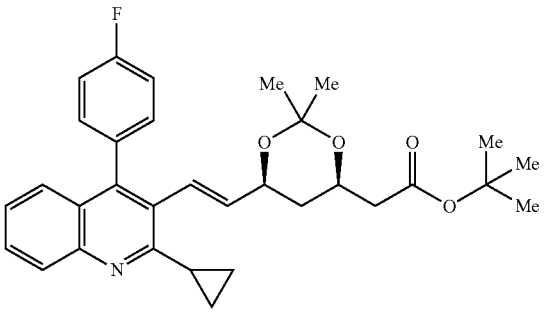
with an aldehyde compound of Formula-III

(III)



in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-II,

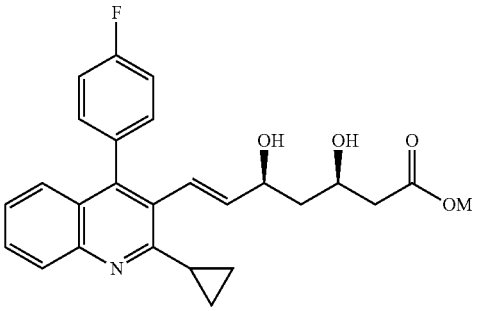
(II)



(b) hydrolyzing the compound of Formula-II under the acidic conditions to remove acetonide protection to form diol compound;

(c) treating the diol compound of step (b) in-situ with an alkali metal hydroxide to form the corresponding alkali metal salt of Pitavastatin (I);

(I)



wherein, M is Na^+, K^+, Li^+;

(d) treating the alkali metal salt of pitavastatin (I) with a magnesium source to obtain pitavastatinmagnesium; and

(e) isolating the pitavastatin magnesium.

The phosphonium bromide compound of Formula-IV and aldehyde compound of Formula-III can be reacted in the presence of alkali or alkaline earth metal bases. The alkali or alkaline earth metal bases comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate and the like. In particular, it may be potassium carbonate.

Embodiments includes that the reaction may be performed in a suitable polar aprotic solvent comprises one or more dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methylpyrrolidone or mixtures thereof. In particular, it may be dimethylsulfoxide. The reaction may be performed at an ambient temperature i.e. at about 15° C. to about 40° C. In particular, it may be from about 20° C. to about 35° C.

The reaction mixture may be stirred for about 5 to 15 hours till completion of the reaction, in particular for 10 hours. The reaction mixture may be further treated with suitable organic solvents like toluene, xylene, methylene dichloride, ethyl acetate for extracting the compound of Formula-II. Particularly, the compound of Formula-II is extracted by using toluene.

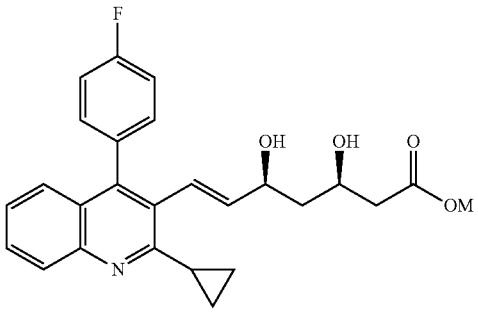
In general, the compound of Formula-II may be isolated by removal of toluene followed by addition of isopropanol. After the addition of isopropanol, the reaction mixture can be heated to 40° C. to 80° C., preferably 60° C. to 70° C. and cooling to 15° C. to obtain olefin compound of Formula (II). The compound of Formula (II) may optionally be purified in suitable polar solvent like methanol, ethanol, Isopropanol, acetone, DMF, ethyl acetate, butyl acetate and the like. In particular, the compound of Formula (II) may be purified using methanol.

Further embodiments of the process include, hydrolysis of compound of Formula (II). The hydrolysis of olefin compound is done under the acidic conditions to remove the acetonide protection and to form diol compound. The suitable acids comprise one or more of hydrochloric acid, acetic acid, sulfuric acid, nitric acid, phosphoric acid and the like. In particular it may be hydrochloric acid.

The diol compound obtained is in-situ treated with an alkali metal hydroxide selected from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like.

In particular it may be sodium hydroxide to obtain corresponding alkali metal salt of pitavastatin (I)

(I)



herein M is Na^+.

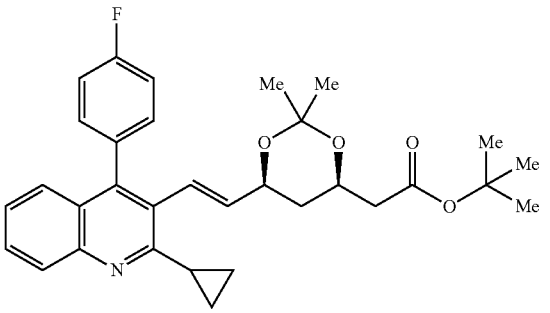
Embodiments of the process includes treating alkali metal salt of formula (I) of pitavastatin, in particular it may bepitavastatinsodium with magnesium source. Preferred magnesium source comprises one or more of magnesium chloride, magnesium methoxide, magnesium acetate and hydrates thereof. In particular, it may be magnesium chloride hexahydrate.

In general, the pitavastatinmagnesium prepared by the method as described above, can be dried in hot air oven at 40° C. to 45° C. for at least about 4 to 24 hours having water content in the range of about 8% to 12% wt/wt to obtain pitavastatinmagnesium in crystalline form.

Embodiments further includes, drying pitavastatin magnesium having water content in the range of about 8% to about 12% wt/wt for about 8 hours or more; in particular, for at least about 24 hours so as obtain substantially anhydrous pitavastatin magnesium having water content less than about 2% wt/wt.

According to the preferred embodiment, there is provided an improved process for the preparation of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2, 2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester of Formula (II),

(II)



the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of Formula-II,

(b) treating compound of Formula-II with one or more suitable polar solvent to form reaction mixture;

(c) heating the reaction mixture at an elevated temperature;

(d) cooling the reaction mixture to ambient temperature; and

(e) isolating the (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester in crystalline form.

The phosphonium bromide compound of Formula-IV and aldehyde compound of Formula-III can be reacted in the presence of alkali or alkaline earth metal base. The alkali or alkaline earth metal base comprises one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate and the like. In particular, it may be potassium carbonate.

Embodiments includes that the reaction can be performed in one or more of suitable polar aprotic solvent selected from dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetrahydrofuran, N-methylpyrrolidone or mixtures thereof. In particular it may bedimethylsulfoxide at an ambient temperature i.e. at about 15° C. to about 40° C. In particularly, it may be from about 20° C. to about 35° C.

The reaction mixture can be stirred for about 5 to 15 hours till completion of the reaction. In particular, it may be for 10 hours. The reaction mixture can be further treated with suitable organic solvents like toluene, xylene, methylene dichloride, ethyl acetate for extracting compound of Formula-II. In particular, the compound of Formula (II) may be extracted with toluene.

The compound of Formula-II can be isolated by removal of toluene followed by addition of isopropanol. After the addition of isopropanol, the reaction mixture can be heated to 40° C. to 80° C., particularly at about 60° C. to 70° C. and cooling to 15° C. to obtain compound of formula (II). The compound of formula (II) can be purified in suitable polar solvent like methanol, ethanol, Isopropanol, acetone, DMF, ethyl acetate, butyl acetate and the like. In particular, it may be methanol.

In general, the term "elevated temperature" includes heating the compound II in a polar solvent at about 50° C. to about 100° C. In particular, the compound II may be heated at about 50° C. to about 70° C., most particularly, at about 60° C. to 65° C.

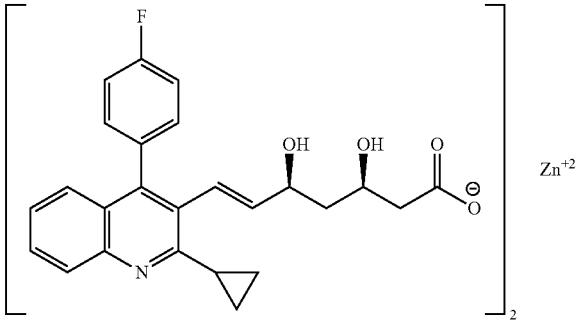
In general, the term "ambient temperature" includes cooling the reaction mixture comprising the compound II in a polar solvent at about 0° C. to about 30° C. In particular, it may be at about 0° C. to about 15° C., most particularly, at about 0° C. to 10° C. According to the embodiment, the compound (II) i.e. (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester is obtain in crystalline form after purification in polar solvent.

The crystalline form of compound (II) is characterized by an X-ray powder diffraction pattern having characteristics peaks expressed in degrees 2θ (±0.2° 20) at 7.86°, 9.94°, 11.48°, 12.71°, 14.80°, 15.88°, 17.44°, 18.16°, 19.17°, 19.97°, 20.77°, 22.71°, 23.41°, 24.68°, 26.02°, 27.63° and 29.36°±0.2°. The X-ray powder diffraction pattern is characterized substantially the same that shown in FIG. **3**.

The crystalline form of compound (II) is characterized by an IR spectrum having peaks at about 2999, 2976, 1720, 1600, 1512, 1487, 1379, 1342, 1288, 1197, 1134, 1066, 1035, 931 and 842 cm^{-1} and DSC endotherm at about 116.04° C. The DSC thermogram is substantially the same that shown in FIG. **4**.

According to the further embodiment, there is provided a process for the preparation of pitavastatinzinc of formula (IC),

(IC)



the process comprising:

(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal base in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-II;

(b) hydrolyzing the compound of Formula-II under the acidic conditions to remove the acetonide protection to form diol compound;

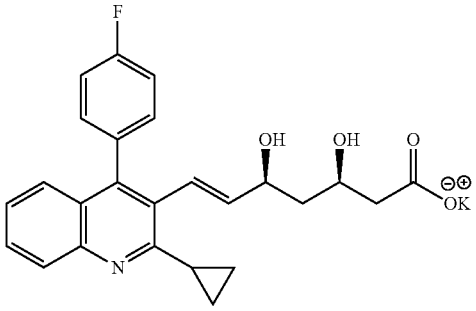
(c) treating the diol compound of step (b) in-situ with an alkali metal hydroxide to form the corresponding alkali metal salt of pitavastatin (I);

(d) treating the alkali metal salt of pitavastatin (I) with a zinc source to obtain Pitavastatinzinc; and
(e) isolating the pitavastatinzinc.

In general, the process parameters for the preparation of compound (II) and its hydrolysis are similar as discloses herein above. The preferable zinc source comprises one or more of zinc formate, zinc acetate, zinc propionate, zinc maleate, zinc fumarate, zinc tartrate, zinc lactate, zinc malate, zinc citrate, Zinc ascorbate, zinc malonate, zinc oxalate, zinc glycolate, zinc methanesulfonate, zinc ethanesulfonate, a salt of zinc with amino acid, zinc sulfate, zinc chloride, zinc carbonate or zinc nitrate. In particular, it comprises one or more of zinc sulfate, zinc chloride or zinc acetate.

According to the further aspect, there is provided a method for the preparation of pitavastatinpotassium of formula (ID),

(ID)



the process comprising:
(a) reacting phosphonium bromide compound of Formula-IV with an aldehyde compound of Formula-III in the presence of an alkali or alkaline earth metal bases in one or more suitable polar aprotic solvent to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of Formula-II,
(b) hydrolyzing the compound of Formula-II by subjecting under the acidic conditions to remove the acetonide protection to form diol compound;
(c) treating the diol compound of step (b) in-situ with a potassium source to obtain pitavastatinpotassium.

In general, the process parameters for the preparation of compound (II) and its hydrolysis are similar as discloses herein above. The preferable potassium source comprises one or more of potassium hydroxide, potassium carbonate, potassium bicarbonate, potassium acetate, potassium chloride and the like.

According to the further embodiment, there is provided a process for the preparation of amorphous form of pitavastatinmagnesium, the process comprising:
(a) providing a solution comprising pitavastatinmagnesium in a suitable organic solvent wherein the organic solvent is selected from the group consisting of a chlorinated solvent, alcoholic solvent, ketonic solvent, esters solvent and mixtures thereof;
(b) removing the organic solvent to obtain residue;
(c) adding a suitable anti-solvent to the residue; and
(d) recovering the amorphous form of the pitavastatinmagnesium.

The amorphous form can be generally prepared by addition of anti-solvent to a concentrated solution of pitavastatinmagnesium in an organic solvent.

Embodiments of the process includes preparing the solution of pitavastatinmagnesium in suitable organic solvent selected from the group consisting of a chlorinated solvent, alcoholic solvent, ketonic solvent, ester solvents and mixtures thereof. The preferred solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, and mixtures thereof or mixture thereof with water. In particular, the suitable solvent comprises one or more of methanol, acetone, ethyl acetate.

In general, the embodiment of the process includes adding suitable antisolvent to the solution of pitavastatinmagnesium in suitable organic solvent. The suitable anti-solvent comprises one or more of hexane, heptane, cyclohexane, toluene, xylene, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, tetrahydrofuran and the like. In particular, the suitable anti-solvent comprises one or more of heptane or cyclohexane or methyl tert-butyl ether.

According to the embodiment, there is provided a process for the preparation of amorphous form of pitavastatinmagnesium, the process comprising:
(a) providing a solution comprising pitavastatinmagnesium in a suitable organic solvent wherein the organic solvent is one or more of a chlorinated solvent, alcoholic solvent, ketonic solvent, esters solvent and mixtures thereof;
(b) heating reaction mixture at an elevated temperature followed by cooling to ambient temperature;
(c) adding a suitable anti-solvent to the solution; and
(d) recovering the amorphous form of pitavastatinmagnesium.

In general, the suitable solvents and anti-solvents comprises from the same as listed herein above. However, the reaction mixture can be heated to an elevated temperature in step (b). The elevated temperature is from about 50° C. to about 100° C. In particularly, it may be from about 70° C. to about 90° C.

The reaction mixture is then cooled to an ambient temperature, preferably from about 15° C. to about 35° C., preferably from about 25° C. to 35° C.

It is preferable that the anti-solvent and solvent are miscible. The amorphous form can also be prepared by lyophilization of or removal of solvent from the solution of pitavastatinmagnesium in a suitable solvent.

According to the further embodiments, there is provided a process for the preparation of amorphous form of pitavastatinmagnesium having water content less than about 2% wt/wt, the process comprising:
(a) providing pitavastatinmagnesium in crystalline form having water content in the range of about 8% to about 12% wt/wt;
(b) contacting the pitavastatinmagnesium with humid air in a fluidized bed drier, or maintaining the pitavastatinmagnesium at a temperature of from about 5 to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 to 5 days; and
(c) recovering the pitavastatin magnesium in the amorphous form having water content less than about 2% wt/wt.

According to the process, amorphous form of pitavastatinmagnesium having water content less than about 2% wt/wt is prepared by contacting pitavastatinmagnesium containing about 8% to about 12% of water content with humid air in a fluidized bed apparatus.

In particular, the temperature is of about 25° C. to about 50° C., more particularly at about 30° C. to about 40° C. The contacting may be carried out, in particularly at about 6 hours to 2 days. As used herein, the term "humid" refers to a relative humidity of at least 30%. In particular, it may be at least about 50% and most particularly at least about 70%.

According to the further embodiment, there is provided substantially pure pitavastatinmagnesium in stable crystalline form.

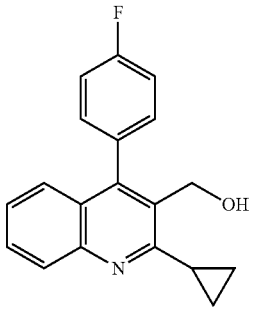
In another embodiment, there is provided pitavastatinmagnesium substantially free desflouro impurity, cis-isomer impurity, pitavastatin 5-oxo impurity, pitavastatinlactone impurity, pitavastatin t-butyl diol ester impurity and pitavastatincondensed impurity when measured by area percentage of HPLC. Also, pitavastatindiastereomeric impurity less than 0.3% by area percentage of HPLC.

According to the further embodiment, there is provided a pharmaceutical composition comprising a therapeutically effective amount of crystalline pitavastatinmagnesium characterized by X-ray diffraction pattern having characteristic peaks at 2-theta values 10.1°, 13.2°, 19.3° and 27.2°±0.2°, and one or more pharmaceutically acceptable carriers, excipients or diluents.

According to the further embodiment, there is provided a pharmaceutical composition comprising a therapeutically effective amount of amorphouspitavastatinmagnesium characterized by x-ray diffraction pattern substantially as depicted in FIG. **2**, and one or more pharmaceutically acceptable carriers, excipients or diluents.

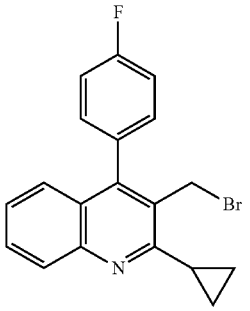
The starting material, phosphonium bromide compound of Formula-IV, can be prepared from alcoholic compound of formula (VI)

(VI)



The alcoholic compound of formula (VI) is converted o phosphonium compound of Formula (IV) via formation of 3-(bromomethyl)-2-cyclopropyl-4(4'-flourophenyl)quinoline of Formula (V) by the known process reported in the prior art. WO 95/11898 A1 in its reference example-7 and Example-1 or as per the process disclosed in U.S. Pat. No. 6,627,636 and U.S. Pat. No. 5,763,675.

(V)

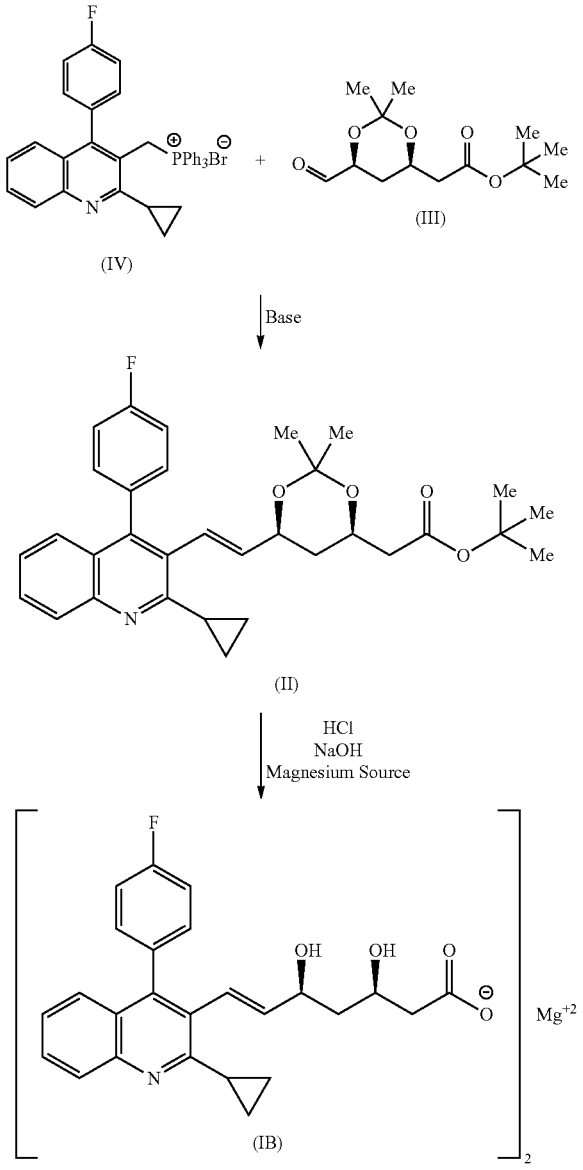


The bromo compound of formula (V) 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline with wittig reagent like triphenyl phosphine in suitable non-polar solvents like toluene, o-xylene, chlorobenzeneetc to obtain phosphonium bromide compound of formula (IV).

The starting reagent, alcohol compound of formula (VI) can be prepared from the known process reported in the art like *Tetrahedron Letters*, Vol. 34, No. 51, p.p. 8271-8274 (1993); *Heterocycles*, Vol. 50, No. 1, 1999*; Drugs of Future* 1998 23 (8) or *Tetrahedron Asymmetry* 1993, Vol. 4, pp. 201-204 are reported herein as reference in its entirety.

As set forth in the following schemes, the pitavastatin magnesium can be prepared by as shown bellow:

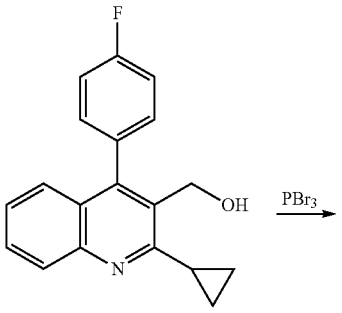
Scheme-1



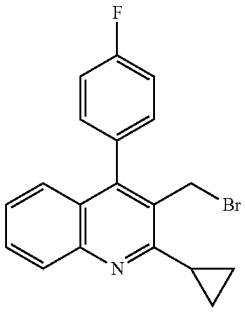
The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Preparation-1

Preparation of 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline (V)



(VI)

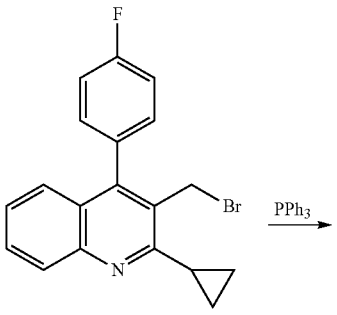


(V)

1 Kg of alcohol compound of formula (VI) and 8 L of methylene dichloride were taken in reactor at 0° C. 0.462 Kg of freshly prepared phosphonium bromide solution in 2 L methylene dichloride was added slowly and stirred at 25° C. for 2 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was quenched with 5% sodium bicarbonate solution to adjust the pH from 7-8. The organic layer was separated and washed with 5 L water followed by removal of solvent under vacuum at 45° C. The residue was treated with 2.5 L heptane at 60° C. and cooled to 15° C. The product was filtered at 15° C. and dried under vacuum at 55° C. for 8 hours to obtain 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline.

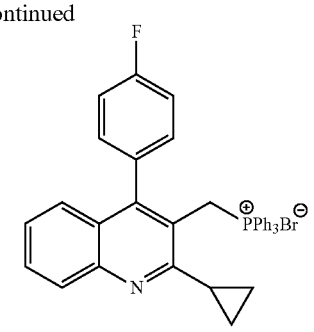
Preparation-2

Preparation of Phosphonium Bromide Compound of Formula (IV)



(V)

-continued

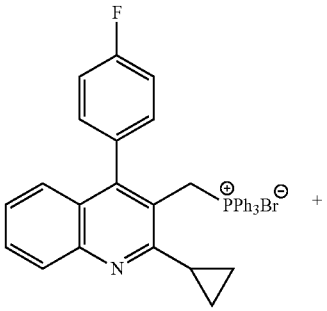


(IV)

1 Kg of 3-(bromomethyl)-2-cyclopropyl-4-(4'-flourophenyl)quinoline, 10 L of toluene and 300 mL of isopropanol were taken in reactor and heated at 50° C. 0.874 Kg of triphenyl phosphine solution in 2 L toluene was added slowly and stirred for 3 hours. The reaction mixture was cooled to 25° C. and stirred for 1 hour. The product was filtered and washed with toluene. The product was dried in tray dryer at 55° C. for 8 hours to obtain phosphonium bromide compound of formula (IV).

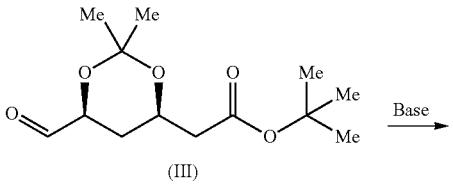
Example-1

Preparation of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester Compound of Formula II

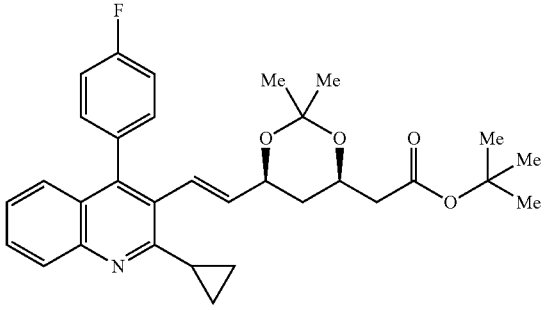


(IV)

+



(III)



(II)

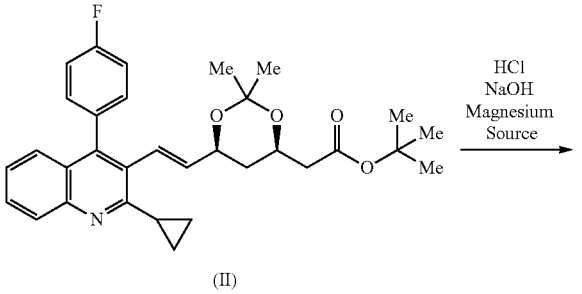
To the solution of 0.751 Kg of tert-butyl-2-((4R,6S)-6-formul-2,2-dimethyl-1,3-dioxan-4-yl)acetate (III) in 7 L of dimethylsulphoxide was added 1 Kg of phosphonium bromide compound of formula (IV) and 0.67 Kg of potassium carbonate. The reaction mixture was stirred at 25° C. for 10 hours. The reaction mixture was quenched with water and extracted with toluene. The organic layer was concentrated and the title compound was isolated using isopropanol as crude solid. The crude product thus obtained was recrystallized in methanol as shown below.

Purification of Olefin Compound of Formula II

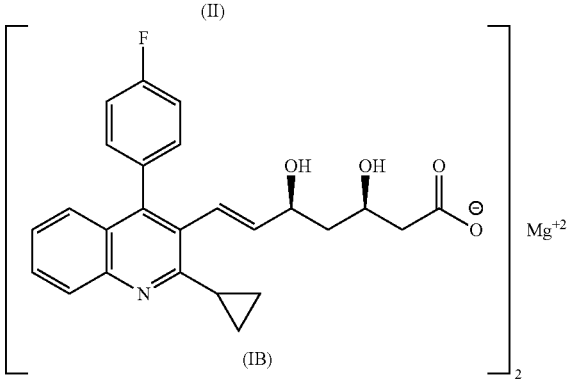
Pitavastatin Olefin compound (II) (100 g) and methanol (600 mL) were heated to 60° C. to 65° C. to obtain the clear solution and stirred for 10 mins. Activated Carbon (10 g) were added at 60° C. to 65° C. and stirred for 10 min. The reaction mixture was filtered and washed with methanol (100 mL). The filtrate was cooled to 25° C. and gradually to 10° C. followed by stirring for 2 hours at 10° C. The resulting slurry was filtered and washed with chilled methanol (100 mL). The wet-cake was heated in methanol (480 mL) at 60° C. to 65° C. to obtain the clear solution. Activated Carbon (10 g) were added at 60° C. to 65° C. and stirred for 10 min. The reaction mixture was filtered and washed with methanol (100 mL). The filtrate was cooled to 25° C. and gradually to 10° C. followed by stirring for 2 hours at 10° C. The resulting slurry was filtered and washed with chilled methanol (100 mL). The wet-cake was dried under vacuum for 30 minutes followed by drying in hot air oven at 50° C. to 55° C. for 12 hours to obtain crystalline olefin compound (II) characterized by X-ray powder diffraction substantially as same as shown in FIG. **3** and DSC thermogram having endothermic peak at about 116.04° C. as shown in FIG. **4**.

Example-2

Preparation of Pitavastatin Magnesium of Formula (IB)



(II)



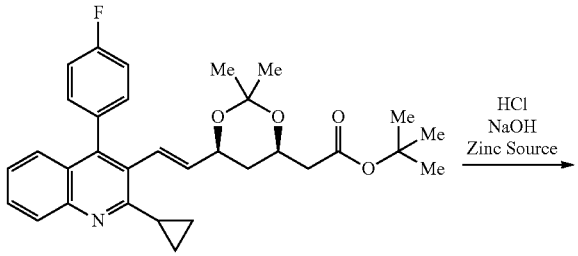
(IB)

To the solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula II (crystalline) in 1 L methanol was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution.

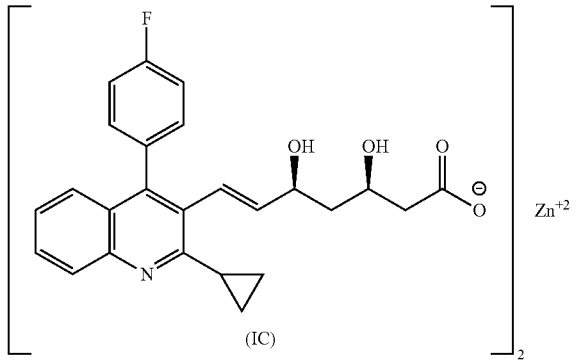
The reaction mixture was stirred for 4 hours at 25° C. and quenched in water. The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH of about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer is treated with 100 g of magnesium chloride hexahydrate and stirred for 30 min at 25° C. The solution is cooled to 15° C., filtered and washed with water. The product is dried in hot air oven for 4 hours to obtain 82 g of crystalline Pitavastatin Magnesium having water content of 11.0%. (XRD as shown in FIG. **1**)

Example-3

Preparation of Pitavastatin Zinc of Formula (IC)



(II)

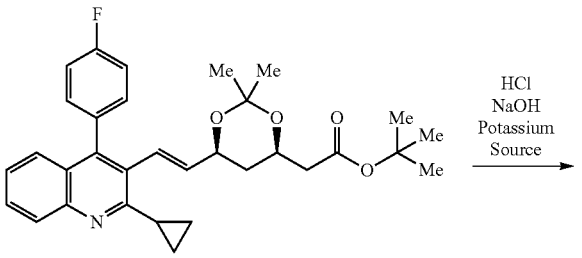


(IC)

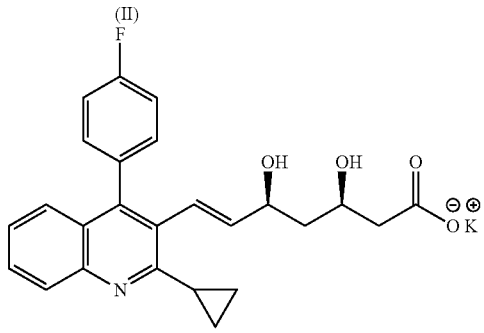
To the solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula II (crystalline) in 1 L methanol was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution. The reaction mixture was stirred for 4 hours at 25° C. and quenched in water. The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH of about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer is treated with 100 g of zinc sulfate and stirred for 30 min at 25° C. The solution is cooled to 15° C., filtered and washed with water. The product is dried in hot air oven for 4 hours to obtain 75 g of crystalline Pitavastatin zinc.

Example-4

Preparation of Pitavastatin Potassium of Formula (ID)



(II)



(ID)

To the solution of 100 g of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-flourophenyl)quinoline-3-yl)-vinyl-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula II (crystalline) in 1 L methanol was added 272.8 mL 1N HCl solution at 25° C. The reaction mixture was stirred for 8 hours. The reaction mixture was cooled to 15° C. and treated with 23.2 g 10% sodium hydroxide solution. The reaction mixture was stirred for 4 hours at 25° C. and quenched in water. The reaction mass was treated with 92 mL 1 N HCl solution to adjust the pH of about 8.0 and treated with methylene dichloride for washing. The separated aqueous layer is treated with 80 g of Potassium hydroxide and stirred for 30 min at 25° C. The solution is cooled to 15° C., filtered and washed with water. The product is dried in hot air oven for 4 hours to obtain 72 g of crystalline Pitavastatin Potassium.

Example 5

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium was dissolved in 800 ml Ethyl Acetate by heating at 75° C. to 80° C. The slightly turbid solution was filtered through hyflow bed at 75° C. to 80° C. The filtrate was cooled to 25° C. and added to cyclohexane (3300 mL). The reaction mixture was stirred for 2 hours. The reaction mixture was filtered and wet-cake was washed with cyclohexane (100 mL). The product was dried in hot air oven for 12 hours to get 83.0 g amorphous Pitavastatin Magnesium. The obtained solid was amorphous as is shown by the X-ray diffraction pattern given in FIG. **2**.

Example 6

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium was dissolved in 800 ml Ethyl Acetate by heating at 75° C. to 80° C. The slightly turbid solution was filtered through hyflow bed at 75° C. to 80° C. The filtrate was distilled under vacuum till dry powder obtained at 45° C. to 50° C. The solid was cooled to 25° C. and cyclohexane (500 mL) was added to the filtrate and stirred for 30 min. The reaction mixture was filtered and wet-cake was washed with cyclohexane (100 mL). The product was dried in hot air oven for 12 hours to get 83.0 g amorphous Pitavastatin Magnesium. The obtained solid was amorphous as is shown by the X-ray diffraction pattern given in FIG. **2**.

Example 7

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium and Methanol (500 mL) were stirred in RBF for 30 minutes. The reaction mixture was distilled at 45° C. to 50° C. under vacuum to obtain dry product. The filtrate was distilled under vacuum till dry powder obtained at 45° C. to 50° C. The solid was cooled to 25° C. and cyclohexane (500 mL) was added to the filtrate and stirred for 30 min. The reaction mixture was filtered and wet-cake was washed with cyclohexane (100 mL). The product was dried in hot air oven for 12 hours to get 83.0 g amorphous Pitavastatin Magnesium.

Example 8

Preparation of the Amorphous Form of Pitavastatin Magnesium

100 g of crystalline Pitavastatin Magnesium was dissolved in 800 ml Acetone by heating at 55° C. to 60° C. The slightly turbid solution was filtered through hyflow bed at 55° C. to 60° C. The filtrate was cooled to 25° C. and added to diisopropyl ether (3000 mL). The reaction mixture was stirred for 3-min. The reaction mixture was filtered and wet-cake was washed with diisopropyl ether (100 mL). The product was dried in hot air oven for 12 hours to get 45.0 g amorphous Pitavastatin Magnesium.

Example 9

Preparation of the Amorphous Form of Pitavastatin Magnesium

10 g of Pitavastatin Magnesium having water content 11% was dried in fluid bed dried at 45° C. for 2 days to obtain amorphous Pitavastatin Magnesium having water content less than 2% wt/wt. An X-ray diffraction study on the product showed it to be amorphous.

Example 10

Preparation of the Amorphous Form of Pitavastatin Magnesium

10 g of Pitavastatin Magnesium having water content 11% was dried in vacuum tray dryer at about 5 to about 60° C.,

under pressure of less than 30 mm/Hg for a period of 24 hours to obtain amorphous Pitavastatin Magnesium having water content less than 2% wt/wt. An X-ray diffraction study on the product showed it to be amorphous, see FIG. **2**.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

ADVANTAGES OF THE INVENTION

1. The present invention provides novel pharmaceutically acceptable salt of alkali metal salts of Pitavastatin.
2. The present invention provides an improved process for the preparation of pitavastatinalkali metal salts.
3. The present invention provides crystalline form of pitavastatinmagnesium having 8% to 12% water content.
4. The present invention also provides amorphous form of pitavastatinmagnesium and process for preparation thereof.
5. The present invention provides amorphous form of pitavastatinmagnesium containing less than about 2% of water content.
6. The process provided is eco-friendly, economically viable and easily scalable on large scale production.

We claim:

1. A process for the preparation of an amorphous form of pitavastatin magnesium, the process comprising:

(a) providing a solution comprising pitavastatin magnesium in a suitable organic solvent wherein the organic solvent is one or more of a chlorinated solvent, alcoholic solvent, ketonic solvent, esters solvent and mixtures thereof;

(b) removing the organic solvent to obtain a residue;

(c) adding a suitable anti-solvent to the residue; and

(d) recovering the amorphous form of the pitavastatin magnesium.

2. The process of claim **1**, wherein the suitable organic solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, and mixtures thereof or mixture thereof with water.

3. The process of claim **1**, wherein the suitable anti-solvent comprises one or more of hexane, heptane, cyclohexane, toluene, xylene, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, and tetrahydrofuran.

4. The process of claim **1**, wherein the recovered amorphous form of pitavastatin magnesium has a water content less than about 5% wt/wt.

5. The process of claim **1**, further comprising forming a pharmaceutical composition comprising the recovered amorphous form of pitavastatin magnesium and one or more pharmaceutically acceptable carriers or excipients.

6. A process for the preparation of amorphous form of pitavastatin magnesium, the process comprising:

(a) providing a solution comprising pitavastatin magnesium in a suitable organic solvent wherein the organic solvent is one or more of a chlorinated solvent, alcoholic solvent, ketonic solvent, esters solvent and mixtures thereof;

(b) heating reaction mixture at an elevated temperature followed by cooling to ambient temperature;

(c) adding a suitable anti-solvent to the solution; and

(d) recovering the amorphous form of the pitavastatin magnesium.

7. The process of claim **6**, wherein the suitable organic solvent comprises one or more of methylene dichloride, ethylene dichloride, chlorobenzene, methanol, ethanol, isopropanol, butanol, acetone, methylethyl ketone, ethyl acetate, butyl acetate, isopropyl acetate, and mixtures thereof or mixture thereof with water.

8. The process of claim **6**, wherein the elevated temperature is from about 50° C. to about 100° C.

9. The process of claim **6**, wherein the ambient temperature is from about 15° C. to about 35° C.

10. The process of claim **6**, wherein the suitable anti-solvent comprises one or more of hexane, heptane, cyclohexane, toluene, xylene, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane, and tetrahydrofuran.

11. The process of claim **6**, wherein the recovered amorphous form of pitavastatin magnesium has a water content less than about 5% wt/wt.

12. The process of claim **6**, further comprising forming a pharmaceutical composition comprising the recovered amorphous form of pitavastatin magnesium and one or more pharmaceutically acceptable carriers or excipients.

13. A process for the preparation of an amorphous form of pitavastatin magnesium having a water content of less than 2% wt/wt, the process comprising:

(a) providing pitavastatin magnesium in crystalline form having water content in the range of about 8% to about 12% wt/wt;

(b) contacting the pitavastatin magnesium with humid air in a fluidized bed drier, or maintaining the pitavastatin magnesium at a temperature of from about 5° C. to about 60° C., under pressure of less than 30 mm/Hg for a period of from about 1 to 5 days; and

(c) recovering the pitavastatin magnesium in the amorphous form having water content less than 2% wt/wt.

14. The process of claim **13**, wherein the humid air refers to a relative humidity of at least 30%.

15. The process as claimed in claim **13**, further comprising forming a pharmaceutical composition comprising the recovered amorphous form of pitavastatin magnesium and one or more pharmaceutically acceptable carriers or excipients.

* * * * *

EXHIBIT G

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Kowa Company, Ltd., Kowa Pharmaceuticals America, Inc., and Nissan Chemical Industries, Ltd., Plaintiffs, v. Zydus Pharmaceuticals (USA) Inc., and Cadila Healthcare Ltd. (dba Zydus Cadila), Defendants.	Civil Action No. _____ **COMPLAINT**

Plaintiffs, Kowa Company, Ltd. ("KCL"), Kowa Pharmaceuticals America, Inc. ("KPA") (collectively, "Kowa"), and Nissan Chemical Industries, Ltd. ("NCI") (Kowa and NCI, collectively, "Plaintiffs") by their undersigned counsel, for their Complaint against defendants Zydus Pharmaceuticals (USA) Inc. ("Zydus USA") and Cadila Healthcare Ltd. (dba Zydus Cadila) ("Zydus Cadila") (collectively, "Zydus"), allege as follows:

Jurisdiction and Venue

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code and arising under 35 U.S.C. §§ 271(e)(2) and 281-283. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(b)-(c) and 1400(b). Personal jurisdiction over the defendants in New York is proper under N.Y. C.P.L.R. §§ 301 and 302(a) and because defendants are doing business in this jurisdiction.

Parties

2. KCL is a Japanese corporation having its corporate headquarters and principal place of business in Aichi, Japan. KPA is a wholly owned U.S. subsidiary of KCL. KPA has its corporate headquarters and principal place of business in Montgomery, Alabama and is organized under the laws of Delaware.

3. NCI is a Japanese corporation having its corporate headquarters and principal place of business in Tokyo, Japan.

4. KCL and NCI are engaged in the business of research, developing, manufacturing, and marketing of a broad spectrum of innovative pharmaceutical products, including Livalo®.

5. Upon information and belief, Zydus USA is incorporated in Delaware having a place of business in Pennington, New Jersey, and is a wholly owned subsidiary of Zydus Cadila.

6. Upon information and belief, Zydus Cadila is a corporation organized and existing under the laws of India having its principal place of business in Gujarat, India. Upon information and belief, Zydus filed 505(b)(2) NDA No. 20-8379 (the "505(b)(2) Application").

7. Upon information and belief, Zydus USA sells generic drugs, manufactured and supplied by Zydus Cadila, throughout the United States, including in at least New York.

8. Upon information and belief, Zydus USA is currently transacting business in the Southern District of New York, at least by making and shipping into this Judicial District, or by using, offering to sell or selling or by causing others to use, offer to sell or sell, pharmaceutical products into this Judicial District.

9. Upon information and belief, Zydus derives substantial revenue from interstate and/or international commerce, including substantial revenue from goods used or consumed or services rendered in the State of New York and the Southern District of New York. Further, Zydus USA and Zydus Cadila have availed themselves of the courts in the state of New York by filing suit in New York. By filing the 505(b)(2) Application, Zydus has committed, and unless enjoined, will continue to commit a tortious act without the state of New York, that Zydus expects or should reasonably expect to have consequences in the State of New York including in this Judicial District.

The New Drug Application

10. KPA sells drug products containing pitavastatin (the "pitavastatin drug product") under the trade name Livalo® in the United States pursuant to the United States Food and Drug Administration's approval of a New Drug Application ("NDA") held by KCL (NDA No. 22-363).

11. Livalo® is approved for use as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

12. The approval letter for Livalo®, with approved labeling, was issued by the FDA on August 3, 2009.

13. Certain amendments to the approved labeling for Livalo® have subsequently been approved.

The Patent in Suit

14. United States Patent No. 6,465,477 ("the '477 patent"), entitled "Stable Pharmaceutical Composition," a true and correct copy of which is appended hereto as **Exhibit A,** was duly issued on October 15, 2002 to inventors Toyojiro Muramatsu, Katsumi Mashita, Yasuo Shinoda, Hironori Sassa, Hiroyuki Kawashima, Yoshio Tanizawa, and Hideatsu Takeuchi, and jointly assigned to plaintiffs KCL and NCI. The '477 patent claims, inter alia, pharmaceutical compositions containing pitavastatin salts.

15. Plaintiffs KCL and NCI have been and still are the owners through assignment of the '477 patent, which expires on December 20, 2016. KPA holds a license from KCL for the '477 patent.

16. In accordance with its license, KPA sells the pitavastatin drug product under the trade name Livalo® in the United States. Sales of Livalo® are made pursuant to approval by the FDA of NDA No. 22-363.

17. Plaintiff KCL manufactures the Livalo® drug products as sold by KPA.

18. Plaintiffs Kowa and NCI will be substantially and irreparably harmed by infringement of the '477 patent (the "Livalo® patent"). There is no adequate remedy at law.

COUNT I
INFRINGEMENT OF THE '477 PATENT UNDER 35 U.S.C. § 271(E)(2)(A)

19. Plaintiffs repeat and incorporate herein by reference the allegations contained in each of the foregoing paragraphs.

20. Upon information and belief, defendant Zydus filed the 505(b)(2) New Drug Application with the Food and Drug Administration ("FDA") under 21 U.S.C. § 355(b) (NDA No. 20-8379) seeking approval to market 1 mg, 2 mg, and 4 mg tablets comprising pitavastatin.

21. By this 505(b)(2) Application filing, Zydus has indicated that it intends to engage, and that there is substantial likelihood that it will engage, in the commercial manufacture, importation, use, offer for sale, and/or sale, or inducement thereof, of Plaintiffs' patented pitavastatin drug product immediately or imminently upon receiving FDA approval to do so. Also by its 505(b)(2) Application filing, Zydus has indicated that its drug product is bioequivalent to Plaintiffs' pitavastatin drug product.

22. By its 505(b)(2) Application filing, Zydus seeks to obtain approval to commercially manufacture, use, import, offer for sale, and/or sell, alleged generic equivalents of Plaintiffs' Livalo® pitavastatin drug product prior to the expiration date of the '477 patent.

23. By a letter dated July 28, 2015 (the "Notice Letter"), Zydus informed Kowa and NCI that Zydus had filed a certification to the FDA, pursuant to 21 U.S.C. § 355(b)(2)(A)(iv). On or about July 28, 2015, KPA received the Notice Letter. On or about July 30, 2015, NCI received the Notice Letter. On or about July 31, 2015, KCL received the Notice Letter.

24. Zydus's Notice Letter, purporting to be Zydus's Notice of Certification under 21 U.S.C. § 355(b)(3)(B), indicates that Zydus intends to manufacture, use, sell, or offer for sale, its proposed pitavastatin drug product prior to the expiration of the '477 patent.

25. The Notice Letter asserts that in Zydus's opinion, "no valid claim of [the '477 patent] . . . will be infringed by the manufacture, use, or sale of the Zydus [505(b)(2)] NDA Product."

26. Zydus's filing of 505(b)(2) NDA No. 20-8379 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, importation, offer for sale and/or sale, or the inducement thereof, of its proposed pitavastatin drug product before the expiration of the '477 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

27. Zydus's manufacture, use, importation, offer for sale, sale, and/or importation of its proposed pitavastatin drug product will directly infringe or induce infringement of at least one claim of the '477 patent under 35 U.S.C. § 271(e)(2)(A).

28. Unless Zydus is enjoined from infringing the '477 patent, plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

WHEREFORE, Plaintiffs request the following relief:

(a) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that making, using, selling, offering to sell and/or importing Zydus's pitavastatin drug product for which it seeks FDA approval or any drug product containing pitavastatin will infringe at least one claim of the Livalo® patent;

(b) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that the making, using, offering for sale, selling and/or importing of Zydus's pitavastatin drug product or any drug product containing pitavastatin, will induce the infringement at least one claim of the Livalo® patent;

(c) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. and an order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval for Zydus to commercially make, use, sell, offer to sell or import its pitavastatin drug product or any drug product containing pitavastatin be no

earlier than the date following the expiration date of the Livalo® patent (as extended, if applicable);

(d) a permanent injunction restraining and enjoining against any infringement by defendants, their officers, agents, attorneys, employees, successors or assigns, or those acting in privity or concert with them, of the Livalo® patent, through the commercial manufacture, use, sale, offer for sale or importation into the United States of Zydus's pitavastatin drug product or any drug product containing pitavastatin, and/or any inducement of or contribution to the same;

(e) Attorneys' fees in this action under 35 U.S.C. § 285; and

(f) Such further and other relief in favor of Plaintiffs and against defendants as this Court may deem just and proper.

Dated: New York, New York
September 10, 2015

Kowa Company, Ltd.,
Kowa Pharmaceuticals America, Inc., and
Nissan Chemical Industries, Ltd.

By their attorneys,

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EXHIBIT H

US009351957B2

(12) **United States Patent**
Khera et al.

(10) **Patent No.: US 9,351,957 B2**
(45) **Date of Patent: May 31, 2016**

(54) **AMORPHOUS FORM OF APREMILAST**

(71) Applicant: **CADILA HEALTHCARE LIMITED**, Ahmedabad, Gujarat (IN)

(72) Inventors: **Brij Khera**, Gujarat (IN); **Kumar Kamlesh Singh**, Gujarat (IN); **Santosh Devidas Diwakar**, Gujarat (IN); **Chetan Jayantibhai Vasava**, Gujarat (IN); **Anil Kumar Shivprasad Tiwari**, Gujarat (IN)

(73) Assignee: **Cadila Healthcare Limited**, Ahmedabad (IN)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/677,110**

(22) Filed: **Apr. 2, 2015**

(65) **Prior Publication Data**

US 2015/0283249 A1 Oct. 8, 2015

(30) **Foreign Application Priority Data**

Apr. 4, 2014 (IN) 1283/MUM/2014

(51) **Int. Cl.**

C07D 209/48	(2006.01)
A61K 31/4035	(2006.01)
A61K 9/14	(2006.01)
A61K 9/16	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/4035*** (2013.01); ***A61K 9/14*** (2013.01); ***A61K 9/146*** (2013.01); ***A61K 9/1652*** (2013.01); ***C07D 209/48*** (2013.01)

(58) **Field of Classification Search**

CPC C07D 209/48

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,020,358	A	2/2000	Muller et al.
7,427,638	B2	9/2008	Muller et al.
7,893,101	B2	2/2011	Muller et al.
2013/0217918	A1	8/2013	Venkateswaralu et al.
2014/0081032	A1	3/2014	Connoly et al.

FOREIGN PATENT DOCUMENTS

WO	WO 2009/120167	10/2009
WO	WO 2012/097116	7/2012
WO	WO 2014/072259	5/2014

Primary Examiner — Shawquia Jackson

(74) *Attorney, Agent, or Firm* — Ladas & Parry LLP

(57) **ABSTRACT**

The present invention provides an amorphous form of apremilast and process for preparation thereof. The present invention also provides a pharmaceutical composition comprising an amorphous apremilast and one or more of pharmaceutically acceptable carriers, excipients or diluents used for the treatment of active psoriatic arthritis.

20 Claims, 3 Drawing Sheets

FIG.1

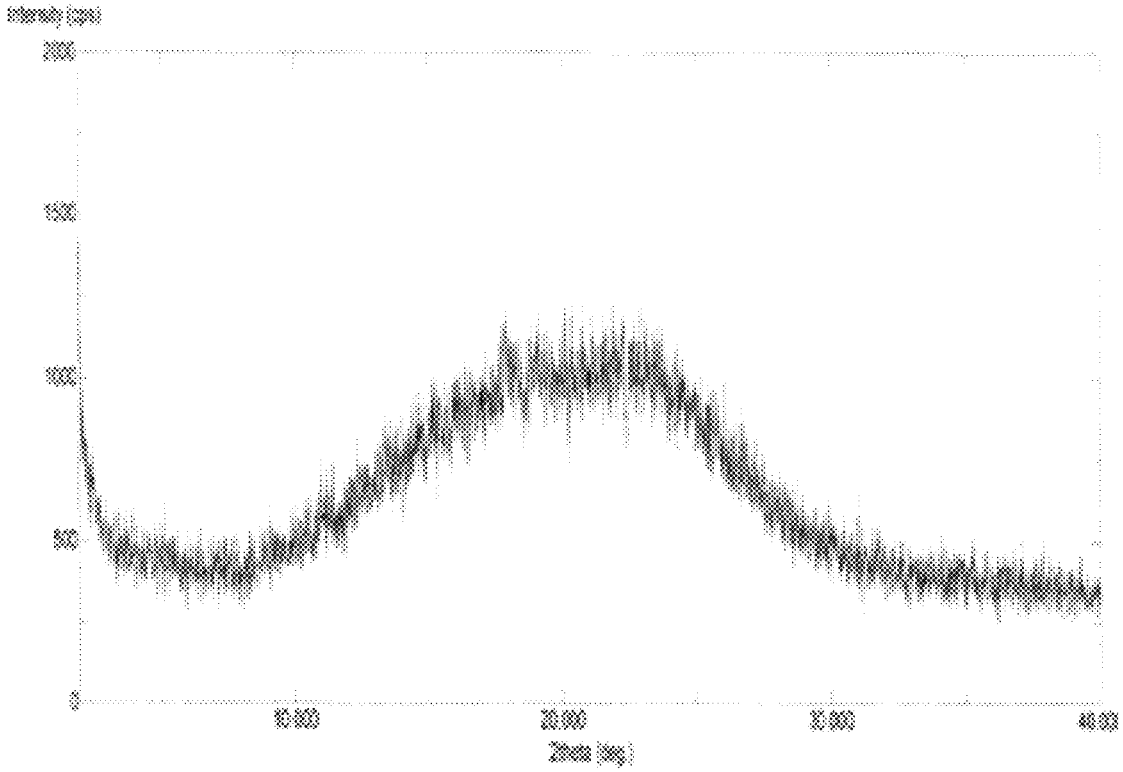


FIG.2

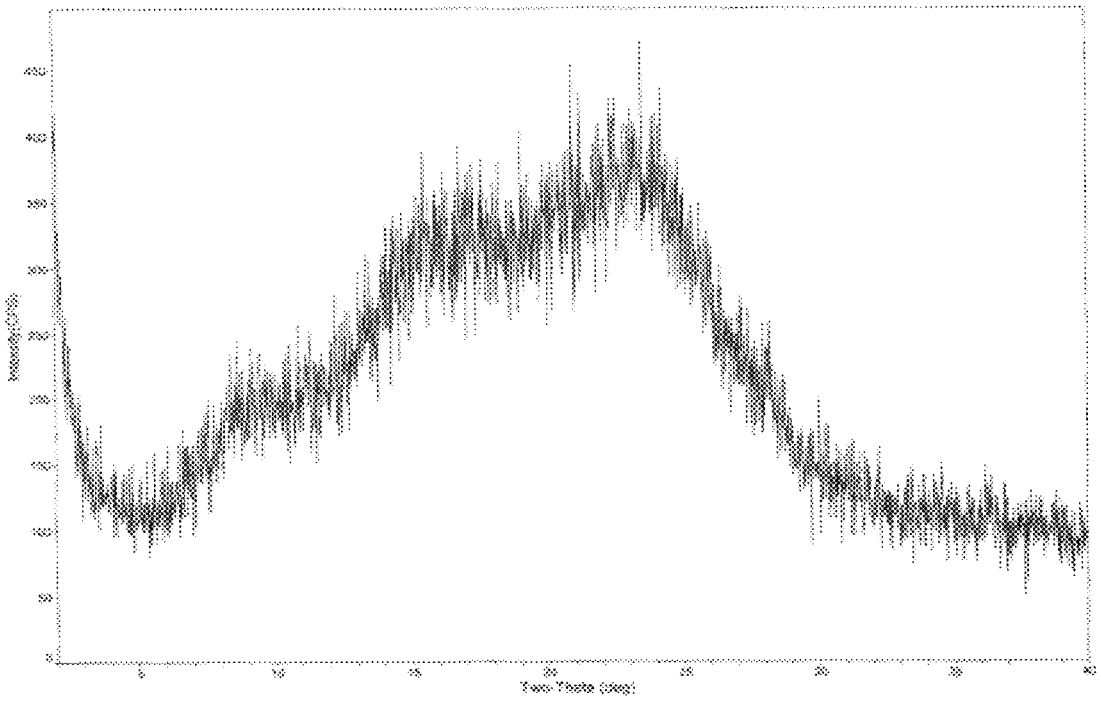
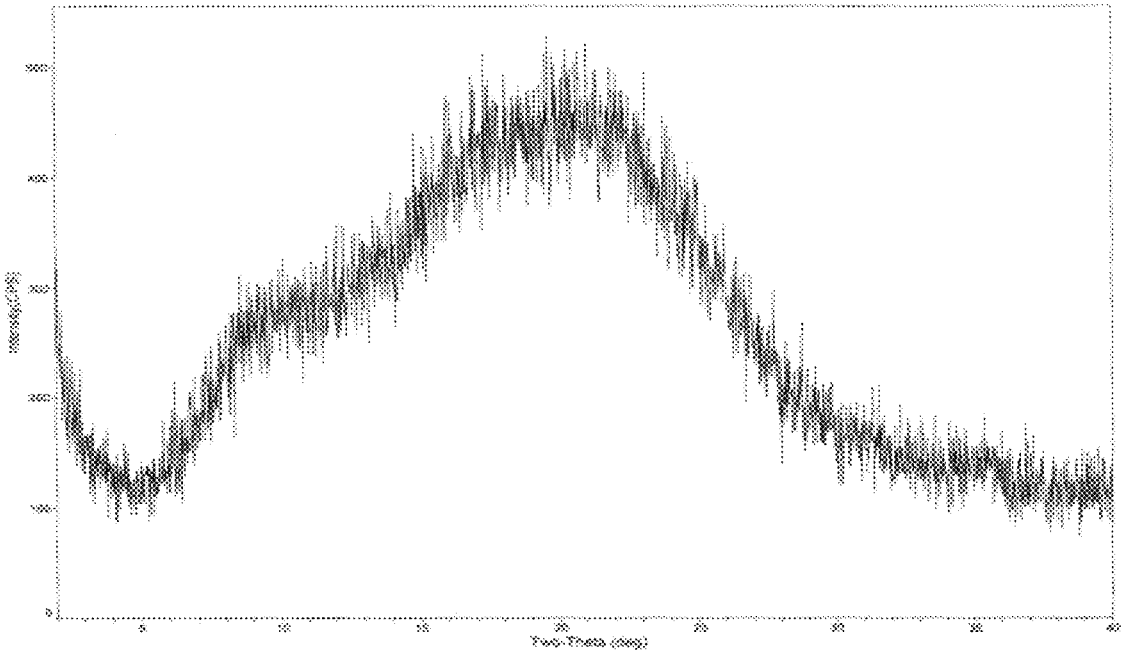


FIG.3



AMORPHOUS FORM OF APREMILAST

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit of Foreign Application INDIA 1283/MUM/2014 filed on Apr. 4, 2014.

FIELD OF THE INVENTION

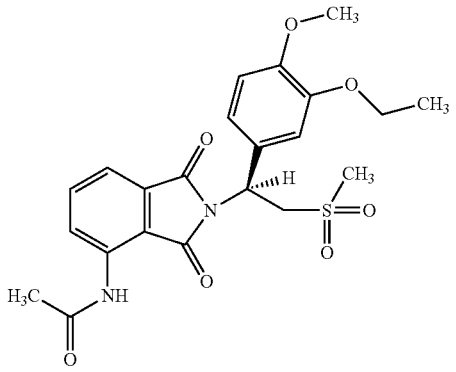
The present invention relates to an amorphous form of apremilast. In particular, the present invention relates to processes for the preparation of amorphous form of apremilast. More particular the present invention relates to the pharmaceutical composition comprising an amorphous apremilast and one or more of pharmaceutically acceptable carriers, excipients or diluents used for the treatment of active psoriatic arthritis.

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. Apremilast is chemically known as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide having Formula (I).

(I)



Apremilast is indicated for the treatment of adult patients with active psoriatic arthritis. It is available under the trade name of OTEZLA® as an inhibitor of phosphodieasterase 4 (PDE4) and OTEZLA tablets are supplied in 10, 20, and 30 mg strengths for oral administration.

U.S. Pat. No. 6,020,358 discloses racemic 2-[1-(3-ethoxy-4-methoxy phenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide and process for its preparation, which is incorporated herein by reference.

U.S. Pat. No. 7,427,638 discloses stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione, substantially free of its (−) isomer, or a pharmaceutically acceptable metabolite, salt, solvate or hydrate, thereof and its pharmaceutical composition. The stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione is the (+)-isomer of racemic

2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide.

WO 2012/097116 and U.S. 2014/0081032 disclose processes for the preparation of isoindoline compounds and their isotopologues including apremilast.

U.S. 2013/0217918 discloses processes for enantioselective preparation of arylmethanesulfonylethylamines using chiral auxiliaries (S)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethylamine which is used for the preparation of apremilast.

WO 2009/120167 and U.S. Pat. No. 7,893,101 disclose various solid forms comprising apremilast include single-component and multiple-component forms, including crystal forms and amorphous forms and their mixture comprising one or more of the Forms A, B, C, D, E, F, G and an amorphous solid form and provides representative XRPD patterns, DSC plots, TGA plots and DVS plots for each of Forms A, B, C, D, E, F and G.

WO 2014/072259 discloses pharmaceutical composition of amorphous apremilast with at least one excipients prepared by melt extrusion technique.

There is no disclosure found about the process for the preparation of an amorphous form of apremilast and its characterization as well as physiochemical properties and its stability.

The different physical properties exhibited by polymorphs affect important pharmaceutical parameters such as storage, stability, compressibility, density and dissolution rates (important in determining bioavailability). Stability differences may result from changes in chemical reactivity (e.g., differential hydrolysis or oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph), mechanical changes (e.g., tablets crumble on storage as a kinetically favored crystalline form converts to thermodynamically more stable crystalline form) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity).

An amorphous form generally provides better solubility and bioavailability than the crystalline form and may be useful for formulations which can have better stability, solubility and compressibility etc which are important for formulation and product manufacturing.

Therefore, it is desirable to have a stable amorphous form of drug with high purity to meet the needs of regulatory agencies and highly reproducible processes for its preparation.

In view of the above, it is therefore, desirable to provide an efficient, more economical, less hazardous and eco-friendly process for the preparation of amorphous form of apremilast. The amorphous form provided herein is stable under ordinary stability conditions with respect to purity and storage.

SUMMARY OF THE INVENTION

In one general aspect, there is provided an amorphous form of apremilast.

In another general aspect, there is provided an amorphous form of apremilast wherein the amorphous apremilast is free from residual solvents.

In another general aspect, there is provided a process for the preparation of an amorphous form of apremilast, wherein the amorphous form is prepared by milling apremilast for sufficient time.

In another general aspect, there is provided an amorphous solid dispersion of apremilast and a polymer.

In another general aspect, there is provided an amorphous solid dispersion of apremilast wherein the amorphous solid

dispersion of apremilast is prepared by a process comprising grinding a solid-solid mixture of apremilast and a polymer.

In another general aspect, there is provided a process for preparing an amorphous solid dispersion of apremilast, wherein the step of grinding a solid-solid mixture of apremilast and a polymer comprises grinding a solid-solid mixture of crystalline apremilast and a polymer.

In another general aspect, there is provided a process for the preparation of an amorphous form of apremilast, the process comprising:

(a) providing a solution of apremilast in one or more of solvents; and

(b) obtaining an amorphous form of apremilast by the removal of the solvent.

In another general aspect, there is provided a stable amorphous form of apremilast wherein the stability is measured by an absence of conversion of the amorphous form of apremilast to a crystalline form of apremilast after the amorphous apremilast is exposed to a relative humidity of 5% at 40° C. or 60% at 25° C. for a period of at least three months.

In another general aspect, there is provided an amorphous solid dispersion of apremilast and a polymer, wherein the amorphous solid dispersion of apremilast is prepared by a process comprising grinding a solid-solid mixture of apremilast and a polymer under controlled humidity.

In another general aspect, there is provided a pharmaceutical composition comprising an amorphous form of apremilast and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect, there is provided a pharmaceutical composition further comprising at least one polymer selected from hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methyl cellulose, methacrylic acid copolymers, and polyvinyl pyrrolidone.

In another general aspect, there is provided a process for packing an amorphous form of apremilast, the process comprising

(a) placing an amorphous apremilast under nitrogen atmosphere in a non-permeable bag and tied;

(b) placing the bag of step (a) inside another bag, optionally containing oxygen busters and sealing it;

(c) optionally placing the bag of step (b) inside a triple laminated bag, optionally containing oxygen busters and sealing it; and

(d) the sealed triple laminated bag inside a high density polyethylene (HDPE) container and sealing it.

In another general aspect, there is provided an amorphous apremilast having particle size distributions wherein the 10^{th} volume percentile particle size (D10) is 50 μm or less, the 50th volume percentile particle size (D50) is 200 μm or less, or the 90th volume percentile particle size (D90) is 400 μm or less, or any combination thereof.

In another general aspect, there is provided an amorphous form of apremilast having a chiral purity of about 95% or more, or about 98% or more, or about 99% or more, or about 99.5% or more, or about 99.8% or more, or about 99.9% or more, as determined using high performance liquid chromatography (HPLC).

In another general aspect, there is provided an amorphous form of apremilast having a purity of about 95% or more, or about 98% or more, or about 99% or more, or about 99.5% or more, or about 99.8% or more, or about 99.9% or more, as determined using high performance liquid chromatography (HPLC).

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

FIG. **1** discloses the x-ray diffractogram (XRD) of the amorphous form of apremilast.

FIG. **2** discloses the x-ray diffractogram (XRD) of the amorphous form of apremilast as per example-4.

FIG. **3** discloses the x-ray diffractogram (XRD) of the amorphous form of apremilast as per example-5.

DETAILED DESCRIPTION OF THE INVENTION

The above and other objects of the present invention are achieved by the process of the present invention, which leads to amorphous apremilast suitable for pharmaceutical use and having greater stability. The invention provides a process for preparing amorphous form of apremilast.

Optionally, the solution, prior to any solids formation, can be filtered to remove any undissolved solids and/or solid impurities prior to the removal of the solvent. Any filtration system and techniques known in the art can be used.

All ranges recited herein include the endpoints, including those that recite a range "between" two values. Terms such as "about", "generally", "substantially," and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

As used herein, the term "controlled humidity" refers to a relative humidity in the range of 50±10%. In particular, the controlled humidity includes grinding process performed under controlled humidity followed by drying under controlled humidity for the preparation of an amorphous form of apremilast.

As used herein, the term "grinder" includes mixers, mills, blenders, and micronizers, or a combination thereof. The terms "grinding", "milling", "mixing", and "blending" and the like are interchangeable for achieving the homogeneous solid-solid mixture.

As used herein, the term "ball milling" as used herein means a process wherein shear forces are applied to a starting material by means of so-called milling balls located in a milling vessel. Typically and preferably, the milling vessel is rotated, wherein the milling balls collide with each other and with the API particles provided as the starting material. The ball mill preferred, may be planetary ball mill with model No. PM 100 and make of Retsch, Germany.

As used herein, the term "stable apremilast" includes an amorphous apremilast measured by an absence of conversion of the amorphous form of apremilast to a crystalline form of apremilast and free from residual solvents after the amorphous apremilast is exposed to a relative humidity of 75% at 40° C. or 60% at 25° C. for a period of at least three months.

As used herein, the term "solid dispersion" means any solid composition having at least two components. In certain embodiments, a solid dispersion as disclosed herein includes apremilast dispersed among at least one other component, for example a polymer.

As used herein the term "immobilize" with reference to the immobilization of the apremilast in the polymer matrix, means that molecules of the apremilast interact with molecules of the polymer in such a way that the molecules of the apremilast are held in the aforementioned matrix and prevented from crystal nucleation due to lack of mobility.

In one general aspect, there is provided an amorphous form of apremilast.

In another general aspect, there is provided an amorphous form of apremilast, wherein the amorphous apremilast is free from residual solvents.

In general, the term "free from residual solvents" herein means residual solvents are within the permissible ICH limits suitable for pharmaceutical preparations. For example but not limited to less than 0.5%, particularly less than 0.3% or more particularly less than 0.2%, or most particularly not in detectable amount.

In another general aspect, there is provided an amorphous form of apremilast, wherein the amorphous form is prepared by milling apremilast for sufficient time. In general, the step of milling apremilast comprises milling crystalline apremilast.

In general, the amorphous form of apremilast is stable and has not detectable quantity of the crystalline form of apremilast after the amorphous form of apremilast is exposed to a relative humidity of 75% at 40° C. or 60% at 25° C. for a period of at least three months.

In another general aspect, there is provided an amorphous solid dispersion of apremilast and a polymer.

In another general aspect, the amorphous solid dispersion of apremilast is prepared by a process comprising grinding a solid-solid mixture of apremilast and a polymer. In general, the step of grinding a solid-solid mixture of apremilast and a polymer comprises grinding a solid-solid mixture of crystalline apremilast and a polymer.

In general, the polymer may be a non-ionic polymer or an ionic polymer. The polymer comprises of hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose, methacrylic acid copolymers, and polyvinylpyrrolidone. In particular, polyvinylpyrrolidone of different grades comprises of K-15, K-30, K-60, K-90 and K-120 which may be used for the preparation of amorphous composition. More particular, hydroxypropylmethyl cellulose acetate succinate and polyvinylpyrrolidone K-30 may be used.

In general, the solid-solid mixture of apremilast and a polymer may be milled by grinding action between two surfaces. Such milling has been traditionally carried out in pharmacy practice by compounding using a pestle and mortar or a common mixer grinder. According to the invention, milling machines that work on substantially the same principle may be used in the present process. Examples of such milling machines include various makes of ball mills, roller mills, gyratory mills, multi-mills, Jet-mills, and the like.

In another aspect, a mill such as a Micros Super Fine Mill, Multi-Mill Sr. No. G.1.132, Retsch (Planetary ball mill), Jet-Mill from Midas Micronizer M-100 Aerosol (No. 154/07-08 or a common mixer grinder can be used. Alternatively another commercially available milling machine can be used.

The process parameter includes adding a solid-solid mixture of apremilast and hydroxypropylmethyl cellulose acetate succinate in a grinder. A specific grinder used can be small-scale to large-scale mixer grinder which can easily prepare the homogeneous mixture of two solids. For example purpose, Quadro dry mixing apparatus for providing lump-free homogenous blending to ensure proper mixing. The varieties of mills and mixers provided in Perry's Chemical Engineers' Handbook Seventh Edition by Robert H. Perry and Don W. Green can be used based on suitability are incorporated herein by reference in its entirety.

This grinding apparatus may consists of a water cooled jacketed bowl with the inside surface made of a suitable material such as Zirconium oxide, stainless steel, tungsten carbide, or aluminum oxide. Depending on the size of the grinder, the speed of rotation of the main shaft and the effective volume of the grinding chamber may vary. The effective volume of the grinding chamber may be in the range from about 0.45 liters to about 30 liters. For low capacity mills (such as 0, capacity 0.45 liters; or 5, capacity 4.8 liters), the speed of rotation of the main shaft is typically in the range from about 200 rpm to about 2000 rpm.

In general aspect, the grinder may be a typical milling apparatus. This milling apparatus may be typically charged with feed material such that from about 10% to 30% of the effective volume of the grinding chamber is occupied. Examples of methods of transferring materials well known in the art include manual transfer, gravity feed, pneumatic conveying (using a high velocity air stream), and vacuum transfer. Such methods, well known in the art, may be used with the process of this invention to charge the feed material into the grinding volume available between the bowl and the sub-shafts. For obtaining homogeneous solid-solid mixture, the apremilast and hydroxypropylmethyl cellulose acetate succinate may be mixed in a wide range of ratios.

The period of milling using the mill may vary depending on the size of the mill, the speed of rotation of the main shaft, the type of feed material, and the quantity of feed material. The effects of these variables are well known in the art and the invention may be worked over a range of these variables. Typically, the period of milling ranges from about 15 minutes to 300 minutes. In general, the apremilast is subjected to grinding involving attrition of the particles and machine surfaces.

In some aspects, the apremilast may be dispersed within a matrix formed by a polymer in its solid state such that it is immobilized in its amorphous form. The polymer may prevent intramolecular hydrogen bonding or weak dispersion forces between two or more drug molecules of apremilast. The solid dispersion provides for a large surface area, thus further allowing for improved dissolution and bioavailability of apremilast.

In some aspects, the ratio of the amount of weight of apremilast within the solid dispersion to the amount by weight of the polymer therein is from about 1:1 to about 1:10. The composition of apremilast with polymer, particularly hydroxypropylmethyl cellulose acetate succinate or polyvinylpyrrolidone may be prepared by using about 1:1 to about 1:10 polymers with respect to apremilast.

In another general aspect, there is provided a process for the preparation of an amorphous solid dispersion of apremilast and a polymer, the process comprising mixing apremilast with a polymer in one or more solvents and obtaining the amorphous solid dispersion of apremilast by the removal of the solvent.

The compound apremilast and a polymer (for example hydroxypropylmethyl cellulose acetate succinate or polyvinylpyrrolidone K-30) may be dissolved in one or more solvents selected from methanol, ethanol, isopropanol, acetone, ethyl acetate or mixture thereof with water. The amorphous solid dispersion may be obtained by the removal of the solvent. The removal of the solvent comprises one or more of evaporation by rotational distillation, evaporation under reduced pressure, spray drying, agitated thin film drying ("ATFD"), freeze drying (lyophilization), flash evaporation, and vacuum distillation thereby leaving the amorphous solid dispersion precipitated in a matrix formed by the polymer.

In another general aspect, there is provided a process for the preparation of an amorphous form of apremilast, the process comprising:

(a) providing a solution of apremilast in one or more of solvents; and

(b) obtaining an amorphous form of apremilast by the removal of the solvent.

Step a) involves providing a solution of apremilast in one or more solvents or mixture thereof.

The solution for step a) can be obtained by the known methods that include:

(i) direct use of a reaction mixture containing apremilast that is obtained in the course of its synthesis; or

(ii) dissolving apremilast in one or more solvents.

The solvents that may be used in step a) comprises one or more of alcohols selected from methanol, ethanol, isopropanol, 2-propanol, 1-butanol, and t-butyl alcohol; ketones selected from acetone, butanone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, t-butyl acetate, and isobutyl acetate, chlorinated hydrocarbons selected from methylene dichloride, ethylene dichloride, and chlorobenzene; acetonitrile; and polar aprotic solvents selected from dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, and mixtures thereof.

Step b) involves isolation of an amorphous form of apremilast from the solution of step a). The isolation may be affected by removing the solvent. The techniques which may be used for the removal of solvent comprises one or more of evaporation by rotational distillation, evaporation under reduced pressure, spray drying, agitated thin film drying ("ATFD"), freeze drying (lyophilization), flash evaporation, and vacuum distillation.

Alternatively, the isolation can be effected by addition of an anti-solvent to the solution obtain in step a), optionally by concentrating the solution obtained in the step.

The anti-solvents comprises one or more of hydrocarbons selected from hexanes, n-heptane, n-pentane, cyclohexane, and methylcyclohexane; aromatic hydrocarbons selected from toluene, xylene, and ethylbenzene; ethers selected diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, and 2-methoxy ethanol.

In another general aspect, there is provided a process of spray drying a solution of apremilast that involves the spray drying of a feed stock, which is prepared as discussed below, wherein any known form of apremilast may be used. The feed stock is dozed into the spray-drying instrument JISL Mini Spray-drier LSD-48 or Lab Ultima Spray-drier and spray drying is carried out under the following parameters.

Sr. No.	Parameters	Conditions
a)	Feed pump	10-50 rpm
b)	Inlet temperature	35°-120° C.
c)	Outlet temperature	30°-100° C.
d)	Aspirator rate	1000-1500 rpm
e)	Vacuum for conveying the dry product	30-120 mm of Hg
f)	Hot air supply	2-4 Kg/cm^2
g)	Atomizer Speed:	40,000-100,000 rpm

In the present invention, feed stock of apremilast is conveniently prepared by dissolving any known forms or wet cake of apremilast in one or more solvents comprises of acetone, C_{1-4}alcohols, C_{2-6}esters, acetonitrile, methylene dichloride, water or mixture thereof. In particular, methanol, ethanol, acetone, ethyl acetate, and methylene dichloride are used or such solvents that evaporate easily to afford dry product.

In another general aspect, there is also provided a process for the preparation of amorphous form of apremilast by spray drying a feed stock comprising apremilast and at least one polymer selected from hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose, methacrylic acid copolymers, and polyvinylpyrrolidone, which is also considered within the scope of invention.

In another general aspect, there is provided a process for the preparation of the amorphous form of apremilast, wherein the amorphous form of apremilast is prepared by grinding a solid-solid mixture of apremilast and hydroxypropyl methylcellulose acetate succinate. In general, grinding the solid-solid mixture is carried out under controlled humidity conditions.

In another general aspect, there is provided a process for the preparation of the amorphous form of apremilast, wherein the amorphous form of apremilast is prepared by grinding a solid-solid mixture of crystalline apremilast and hydroxypropyl methylcellulose acetate succinate.

In another general aspect, there is provided a stable amorphous form of apremilast which is at least stable during storage and drying.

In another general aspect, there is provided a stable amorphous form of apremilast wherein the stability is measured by an absence of conversion of the amorphous form of apremilast to a crystalline form of apremilast after the amorphous apremilast is exposed to a relative humidity of 75% at 40° C. or 60% at 25° C. for a period of at least three months.

In another general aspect, there is provided a process for packing an amorphous form of apremilast, the process comprising

(a) placing an amorphous apremilast under nitrogen atmosphere in a non-permeable bag and tied;

(b) placing the bag of step (a) inside another bag, optionally containing oxygen busters and sealing it;

(c) optionally placing the bag of step (b) inside a triple laminated bag, optionally containing oxygen busters and sealing it; and

(d) placing the sealed triple laminated bag inside a high density polyethylene (HDPE) container and sealing it.

In another general aspect, there is provided an amorphous apremilast having particle size distributions wherein the 10^{th} volume percentile particle size (D10) is 50 μm or less, the 50th volume percentile particle size (D50) is 200 μm or less, or the 90th volume percentile particle size (1)90) is 400 μm or less, or any combination thereof. In particular, D90 is 100 μm or less and D50 is 50 μm or to less.

In another general aspect, there is provided an amorphous form of apremilast having a chiral purity of about 95% or more, or about 98% or more, or about 99% or more, or about 99.5% or more, or about 99.8% or more, or about 99.9% or more, as determined using high performance liquid chromatography (HPLC).

In another general aspect, there is provided an amorphous form of apremilast of having a purity of about 95% or more, or about 98% or more, or about 99% or more, or about 99.5% or more, or about 99.8% or more, or about 99.9% or more, as determined using high performance liquid chromatography (HPLC).

In further aspect, the apremilast may be micronized to achieve the better particle size distribution in order to make suitable Formulation.

The apremilast may be micronized prior to compression and shearing. Micronisation may be by any known method. Micronization is the process of reducing the average diameter of a solid material's particles, for example by milling or grinding. In one aspect an apremilast that has been subjected to a mechanical process which applies sufficient force to the apremilast that the process is capable of breaking coarse particles down to fine particles.

In another aspect micronization of the apremilast may be achieved using one or a combination of the following methods: ball milling, jet milling, jet blending, high-pressure homogenation, or any other milling method.

Ball milling is a milling method used in many of the prior art co-milling processes. Centrifugal and planetary ball milling may also be used.

Jet mills are capable of reducing solids to particle sizes in the low-micron to submicron range. The grinding energy is created by gas streams from horizontal grinding air nozzles. Particles in the fluidised bed created by the gas streams are accelerated towards the centre of the mill, colliding within. The gas streams and the particles carried in them create a violent turbulence and, as the particles collide with one another, they are pulverized.

Alternatively micronized apremilast may be produced by using a high energy media mill or an agitator bead mill, for example, the Netzsch high energy media mill, or the DYNO-mill (Willy A. Bachofen A G, Switzerland).

Powder X-ray Diffraction of amorphous apremilast can be obtained under following conditions.

X-ray powder diffraction spectrum was observed on a MF 2100 2KW X-ray Powder diffractometer of make Rigaku or PANalytical or equivalent having a Copper Kα-radiation at a voltage of 40 kV and 30 mA. Approximately 150 mg sample was gently flattened on a quartz plate without further processing (e.g. Grinding and sieving) and scanned from 2° to 40° at 0.010° sampling width.

According to another aspect, apremilast to be used herein as the starting material may be prepared by the known methods reported in the prior art i.e. by using the processes described in prior art for example, U.S. Pat. No. 6,020,358 and U.S. Pat. No. 6,962,940 which are incorporated herein as reference. The apremilast used as starting material can be of any known crystalline forms reported in the art.

The invention also encompasses pharmaceutical compositions comprising apremilast of the invention. As used herein, the term "pharmaceutical compositions" includes pharmaceutical formulations like tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Pharmaceutical compositions containing the apremilast of the invention may be prepared by using diluents or excipients such as fillers, bulking agents, binders, wetting agents, disintegrating agents, surface active agents, and lubricants. Various modes of administration of the pharmaceutical compositions of the invention can be selected depending on the therapeutic purpose, for example tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

In another general aspect, there is provided a pharmaceutical composition comprising an amorphous form of apremilast and one or more pharmaceutically acceptable carriers, excipients and diluents.

In another general aspect, there is provided a pharmaceutical composition comprising an amorphous form of apremilast and one or more pharmaceutically acceptable carriers, excipients and diluents. In general, the pharmaceutical composition comprising an amorphous form of apremilast comprises at least one polymer selected from hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methyl cellulose, methacrylic acid copolymers, and polyvinyl pyrrolidone.

In another general aspect, there is provided a pharmaceutical composition comprising an amorphous form of apremilast free from residual solvents and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect, there is provided a pharmaceutical composition comprising a stable amorphous form of apremilast and at least one polymer having one or more pharmaceutically acceptable carriers, excipients or diluents.

The present invention is further illustrated by the following example which is provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1

Preparation of Amorphous Apremilast

In 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Apremilast (0.5 gm), polyvinyl pyrrolidone K-30 (4 gm) and 88% methanol in water (12.5 ml) were heated to 65-70° C. to obtain solution. The reaction mixture was stirred for 1 hour, concentrated under vacuum at 65-70° C. and degassed under vacuum for 1 hour at 70° C. to obtain the title compound in pure amorphous form.

Example 2

Preparation of Amorphous Apremilast

In 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Apremilast (2 gm) and polyvinyl pyrrolidone K-30 (4 gm) were grinded in grinding bowl by using planetary ball milling (1 hour milling by 10 min interval every 15 min grinding at RPM 200). Further, the same material mixed in grinding bowl by using planetary ball milling (1 hour milling by 10 min interval every 15 min grinding at RPM 200) to obtain the title compound in pure amorphous form.

Example 3

Preparation of Amorphous Apremilast

In 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Apremilast (2 gm) was grinded in grinding bowl by using planetary ball milling (1 hour milling by 10 min interval every 15 min grinding at RPM 200). Further, the same material mixed in grinding bowl by using planetary ball milling (1 hour milling by 10 min interval every 15 min grinding at RPM 200) to obtain the title compound in pure amorphous form.

Example-4

Preparation of Amorphous Apremilast

In 100 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Apremilast (0.5 gm) and hydroxypropyl methylcellulose (0.5 gm) in 90% ethanol in water (15 mL, 30V) were heated at 65 to 70° C. to obtain solution. The content was stirred for 30 minutes at 25° C. to 30° C. To this, 1.0 g charcoal was added and stirred for 30 minutes at 80° C. The content was filtered through hyflosupercell, and the hyflosupercell pad is washed with 50 mL ethanol. The filtrate was spray dried in JISL Mini spray drier LSD-48 under the below conditions.

Sr. No	Parameters	Conditions
a)	Feed pump	10 rpm
b)	Inlet temperature	100° C.
c)	Outlet temperature	85° C.
d)	Hot air supply	2 Kg/cm^2

The product was collected from cyclone and was further dried at 40° C.±5° C. under vacuum for 4 hours to obtain 4 gm of amorphous form of apremilast. The obtained product is free from residual solvents.

Example-5

Preparation of Amorphous Apremilast

In 250 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Apremilast (9 gm) and methylene dichloride (90 mL) were stirred to prepare the feed stock. The content was filtered through hyflosupercell, and the hyflosupercell pad is washed with 50 mL methylene dichloride. The filtrate was spray dried in Lab Ultima spray drier under the below conditions.

Sr. No	Parameters	Conditions
a)	Feed pump	10 rpm
b)	Inlet temperature	100° C.
c)	Outlet temperature	85° C.
d)	Hot air supply	2 Kg/cm^2

The product was collected from cyclone and was further dried at 40° C.±5° C. under vacuum for 4 hours to obtain 4 gm of amorphous form of apremilast. The obtained product is free from residual solvents.

Example 6

Preparation of Amorphous Apremilast

In 250 mL three necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Apremilast (2.5 g) and hydroxypropyl methylcellulose (2.5 gm) were grinded in grinding bowl by using planetary ball milling (1 hour milling by 10 min interval every 15 min grinding at RPM 300). Further, the same material mixed in grinding bowl by using planetary ball milling (1 hour milling by 10 min interval every 15 min grinding at RPM 300) to obtain 3.75 g of pure amorphous form of apremilast. The obtained product is free from residual solvents.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. An amorphous form of apremilast.

2. The amorphous form of apremilast according to claim **1**, wherein the amorphous apremilast is free from residual solvents.

3. The amorphous form of apremilast according to claim **1**, wherein the amorphous form is prepared by milling apremilast for sufficient time.

4. The amorphous form of apremilast according to claim **3**, wherein the step of milling apremilast comprises milling crystalline apremilast.

5. The amorphous form of apremilast according to claim **1**, wherein the amorphous apremilast is stable and has no detectable quantity of the crystalline form of apremilast after the amorphous form of apremilast is exposed to a relative humidity of 75% at 40° C. or 60% at 25° C. for a period of at least three months.

6. An amorphous solid dispersion of apremilast and a polymer, wherein the polymer is a non-ionic polymer or an ionic polymer comprising one or more of hydroxypropyl methylcellulose acetate succcinate, hydroxypropyl methylcellulose, methacrylic acid copolymers, and polyvinyl pyrrolidone.

7. The amorphous solid dispersion of apremilast according to claim **6**, wherein the amorphous solid dispersion of apremilast is prepared by a process comprising grinding a solid-solid mixture of apremilast and the polymer.

8. The amorphous solid dispersion of apremilast according to claim **7**, wherein the step of grinding a solid-solid mixture of apremilast and a polymer comprises grinding a solid-solid mixture of crystalline apremilast and the polymer.

9. A process for the preparation of an amorphous form of apremilast, the process comprising:

(a) providing a solution of apremilast in one or more of solvents; and

(b) obtaining the amorphous form of apremilast by the removal of the solvent.

10. The process according to claim **9**, wherein the solvent comprises one or more of alcohols selected from methanol, ethanol, isopropanol, 2-propanol, 1-butanol, and t-butyl alcohol; ketones selected from acetone, butanone, and methyl isobutyl ketone; esters selected from ethyl acetate, isopropyl acetate, t-butyl acetate, and isobutyl acetate, chlorinated hydrocarbons selected from methylene dichloride, ethylene dichloride, and chlorobenzene; acetonitrile; and polar aprotic solvents selected from dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, and mixtures thereof.

11. The process according to claim **9**, wherein the removal of the solvent comprises one or more of evaporation, evaporation by rotational distillation device, evaporation under reduced pressure, spray drying, agitated thin film drying ("ATFD"), freeze drying (lyophilization), flash evaporation, and vacuum distillation.

12. A process for the preparation of an amorphous form of apremilast, wherein the amorphous form of apremilast is prepared by grinding a solid-solid mixture of apremilast and hydroxypropyl methylcellulose acetate succcinate.

13. The process according to claim **12**, wherein grinding the solid-solid mixture is carried out under controlled humidity conditions.

14. The process according to claim **12**, wherein the step of grinding a solid-solid mixture of apremilast and hydroxypropyl methylcellulose acetate succcinate comprises grinding a solid-solid mixture of crystalline apremilast and hydroxypropyl methylcellulose acetate succcinate.

15. A pharmaceutical composition comprising an amorphous form of apremilast and one or more pharmaceutically acceptable carriers, excipients or diluents.

16. The pharmaceutical composition according to claim **15** further comprising at least one polymer selected from hydroxypropyl methylcellulose acetate succcinate, hydroxypropyl methylcellulose, methacrylic acid copolymers, and polyvinyl pyrrolidone.

17. A stable amorphous form of apremilast wherein the stability is measured by an absence of conversion of the amorphous form of apremilast to a crystalline form of apremilast after the amorphous apremilast is exposed to a

relative humidity of 75% at 40° C. or 60% at 25° C. for a period of at least three months.

18. An amorphous solid dispersion of apremilast and a polymer, wherein the amorphous solid dispersion of apremilast is prepared by a process comprising grinding a solid-solid mixture of apremilast and a polymer selected from a non-ionic polymer or an ionic polymer comprising one or more of hydroxypropyl methylcellulose acetate succcinate, hydroxypropyl methylcellulose, methacrylic acid copolymers, and polyvinyl pyrrolidone under controlled humidity.

19. The dispersion according to claim **18**, wherein the controlled humidity is a relative humidity in the range of 50±10%.

20. The dispersion according to claim **18**, wherein the step of grinding a solid-solid mixture of apremilast and the polymer comprises grinding a solid-solid mixture of crystalline apremilast and hydroxypropyl methylcellulose acetate succinate.

* * * * *

EXHIBIT I

Crystal Fisher

General Counsel & Compliance Officer

Summary

N/A

Experience

General Counsel & Compliance Officer at Zydus Pharmaceuticals USA, Inc.
July 2017 - Present

Assistant General Counsel at AmerisourceBergen
January 2014 - June 2017 (3 years 6 months)

Senior Manager at Teva Pharmaceuticals
January 2012 - December 2013 (2 years)

Attorney
April 2008 - December 2011 (3 years 9 months)

Attorney
June 2005 - December 2007 (2 years 7 months)

Education

Temple University - James E. Beasley School of Law
J.D., 2001 - 2004
Penn State University
1996 - 2000

Crystal Fisher

General Counsel & Compliance Officer

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